I drew 2 STR's for the claim 6 STR. The 1st covers cpds w/out rings.

The 2nd search covers cpds with rings.

The 2 answer sets were combined & then searched for the claimed method

```
=> file reg
FILE 'REGISTRY' ENTERED AT 14:23:10 ON 17 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   16 JUL 2003  HIGHEST RN 549206-78-2
DICTIONARY FILE UPDATES:  16 JUL 2003  HIGHEST RN 549206-78-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d que stat l23
L7                  STR
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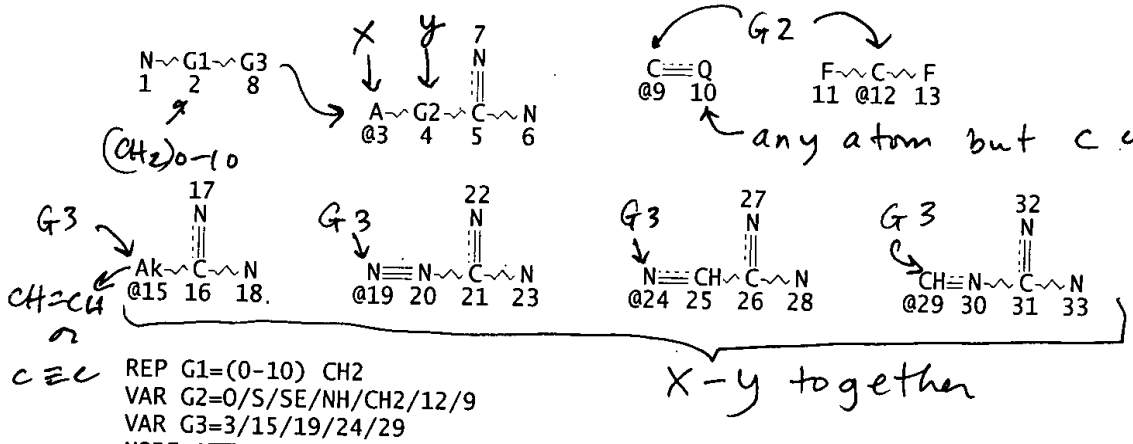
A = any atom but H

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REP G1=(0-10) CH2
VAR G2=O/S/SE/NH/CH2/12/9
VAR G3=3/15/19/24/29
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN  UNS  AT  15
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E2 C  AT  15

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  32

STEREO ATTRIBUTES: NONE
L8       339498 SEA FILE=REGISTRY ABB=ON  PLU=ON  N>2 NOT (RSD/FA OR PMS/CI)
L10        4660 SEA FILE=REGISTRY SUB=L8 SSS FUL L7
L11           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  AGMATINE/CN
L12        4659 SEA FILE=REGISTRY ABB=ON  PLU=ON  L10 NOT L11
L23       13605 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
```

no rings — no polymers

4660 cpds

subtracting out agmatine

4659 cpds

13,605 cites for L12 cpds

```
=> d que stat l24
L1              SCR 1994
L2              SCR 2043 OR 2026 OR 2016
L3              SCR 1428 OR 1432
L4  (   1699388)SEA FILE=REGISTRY ABB=ON  PLU=ON  NRS<4 AND NR<3 AND NR>0 AND
                N>2 NOT (PMS/CI OR SI/ELS OR P/ELS)
L5              STR
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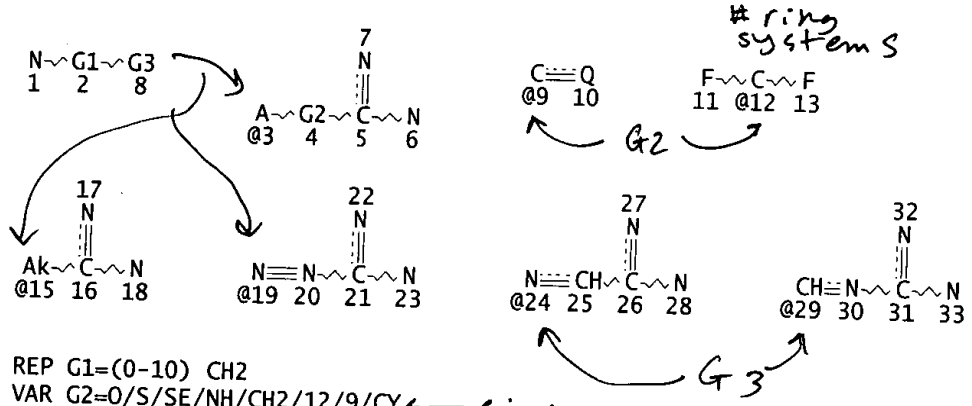


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REP G1=(0-10) CH2
VAR G2=O/S/SE/NH/CH2/12/9/CY
VAR G3=3/15/19/24/29
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN  UNS  AT  15
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E2 C  AT  15

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  32

STEREO ATTRIBUTES: NONE
L6          17608 SEA FILE=REGISTRY SUB=L4 SSS FUL L5 AND L1 AND L3 NOT L2
L21             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  51481-61-9
L22         17607 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L21
L24         12831 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22

=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 14:23:42 ON 17 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 17 Jul 2003  VOL 139 ISS 3
FILE LAST UPDATED: 16 Jul 2003  (20030716/ED)
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This file contains CAS Registry Numbers for easy and accurate substance identification.

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L2              SCR 2043 OR 2026 OR 2016
L3              SCR 1428 OR 1432
L4  (   1699388)SEA FILE=REGISTRY ABB=ON  PLU=ON  NRS<4 AND NR<3 AND NR>0 AND
                N>2 NOT (PMS/CI OR SI/ELS OR P/ELS)
L5              STR
L6        17608 SEA FILE=REGISTRY SUB=L4 SSS FUL L5 AND L1 AND L3 NOT L2
L7              STR
L8       339498 SEA FILE=REGISTRY ABB=ON  PLU=ON  N>2 NOT (RSD/FA OR PMS/CI)
L10        4660 SEA FILE=REGISTRY SUB=L8 SSS FUL L7
L11           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  AGMATINE/CN
L12        4659 SEA FILE=REGISTRY ABB=ON  PLU=ON  L10 NOT L11
L21           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  51481-61-9
L22       17607 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L21
L23       13605 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 <- cites for cpds w/o rings
L24       12831 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 <-  "   "   "  with rings
L25         114 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L23 OR L24) AND (?SEIZUR? OR
                ?CONVULS? OR ?EPILEPS?)
L28          24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L23 OR L24)(L)(?SEIZUR? OR
                ?CONVULS? OR ?EPILEPS?)
L32          15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND EPILE?/OBI   OBI = all search fields
L33          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32 NOT L28                except the
L34           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND  ?EPILE?/AB  5 cites   abstract

=> d que nos l35
L1              SCR 1994
L2              SCR 2043 OR 2026 OR 2016
L3              SCR 1428 OR 1432
L4  (   1699388)SEA FILE=REGISTRY ABB=ON  PLU=ON  NRS<4 AND NR<3 AND NR>0 AND
                N>2 NOT (PMS/CI OR SI/ELS OR P/ELS)
L5              STR
L6        17608 SEA FILE=REGISTRY SUB=L4 SSS FUL L5 AND L1 AND L3 NOT L2
L7              STR
L8       339498 SEA FILE=REGISTRY ABB=ON  PLU=ON  N>2 NOT (RSD/FA OR PMS/CI)
L10        4660 SEA FILE=REGISTRY SUB=L8 SSS FUL L7
L11           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  AGMATINE/CN
L12        4659 SEA FILE=REGISTRY ABB=ON  PLU=ON  L10 NOT L11
L21           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  51481-61-9
L22       17607 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L21
L23       13605 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L24       12831 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22
L35          28 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L23 OR L24)(L)(?SEIZUR? OR
                ?CONVULS? OR ?EPILEP?)  28 cites

=> d que nos l43
L36 (        31)SEA FILE=HCAPLUS ABB=ON  PLU=ON  306-60-5D   <- derivatives of agmatine
L37 (     91404)SEA FILE=HCAPLUS ABB=ON  PLU=ON  NERVOUS SYSTEM+PFT/CT     CT = controlled
L38 (      1680)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEIZURES+PFT/CT                terminology
L39 (     12939)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTICONVULSANTS+PFT/CT
L40 (     10020)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EPILEPSY/OBI          PFT = old, new or
L41 (    337944)SEA FILE=HCAPLUS ABB=ON  PLU=ON  BRAIN+PFT/CT                 "used for" terms
L42 (      1735)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ELECTROCONVULS?
L43           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 AND (L37 OR L38 OR L39 OR  2 cites
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L40 OR L41 OR L42)

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=> d que nos 145
L44 (       877)SEA FILE=HCAPLUS ABB=ON  PLU=ON  306-60-5/RN
L45           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L44 AND (?SEIZUR? OR ?CONVULS?
                OR ?EPILEPS?)

=> s l34-35 or l43 or l45
L60         38 (L34 OR L35) OR L43 OR L45
```

← agmatine

7 cites

38 cites total

=> d ibib abs hitstr l60 1

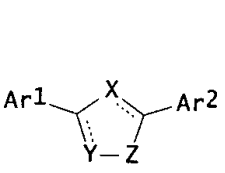
L60 ANSWER 1 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:222333 HCAPLUS
DOCUMENT NUMBER: 138:255233
TITLE: Heteropolycyclic compounds, particularly pyridyl- and phenyl-substituted 1,2,4-oxadiazoles and analogs, and their use as metabotropic glutamate receptor antagonists for inhibiting neuronal damage
INVENTOR(S): Van Wagenen, Bradford; Stormann, Thomas M.; Moe, Scott T.; Sheehan, Susan M.; McLeod, Donald A.; Smith, Daryl L.; Isaac, Methvin Benjamin; Slassi, Abdelmalik
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 151 pp., Cont.-in-part of Appl. No. PCT/US00/22618.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003055085	A1	20030320	US 2002-76618	20020219
WO 2001012627	A1	20010222	WO 2000-US22618	20000818

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-149464P P 19990819
WO 2000-US22618 A2 20000818
US 2001-269847P P 20010221

OTHER SOURCE(S): MARPAT 138:255233
GI



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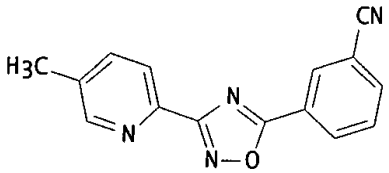


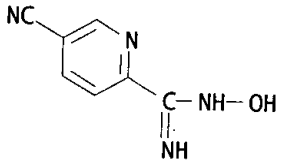
II

AB The title compds. [I; X, Y, Z = N, O, S, CR1 and at least one of X, Y, and Z = heteroatom; R1 = H, alkyl, CF3, etc.; Ar1, Ar2 = (un)substituted (hetero)aryl] that act as antagonists at metabotropic glutamate receptors, and that are useful for treating neurol. diseases and disorders, were prepd. The compds. I exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, notably mGluR5. In particular, medical conditions assocd. with metabotropic glutamate receptors and therefore targeted by the invention compds. include stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia,

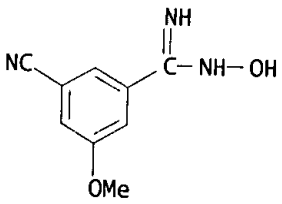
epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease. Several hundred specific examples are individually prepd. and/or claimed. A variety of intermediates were also prepd. For instance, 5-methylpyrid-2-ylamidoxime was prepd. from 2-bromo-5-methylpyridine by Zn- and Pd-complex-mediated cyanation (56%) and reaction of the resulting nitrile with NH2OH.HCl (60%). Cyclization of the amidoxime with 3-cyanobenzoyl chloride (86%) gave invention compd. II. In a bioassay for mGluR5 antagonism in primary astrocyte cultures from rats, the invention compds. I had IC50 values in the range of 11 to 9140 nM.

IT **453565-48-5P**, 5-Cyanopyrid-2-ylamidoxime **453565-51-0P**, 3-Cyano-5-methoxyphenylamidoxime **453565-54-3P**, 3-Cyano-5-fluorophenylamidoxime **453565-57-6P**, 3-Cyano-5-methylphenylamidoxime **453565-58-7P**, 3-Cyanophenylamidoxime **453565-60-1P**, 3-Cyano-5-dimethylaminophenylamidoxime **453565-61-2P**, 6-Cyanopyrid-2-ylamidoxime **453566-11-5P**, 6-Cyano-4-methoxypyrid-2-ylamidoxime
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor antagonists for inhibiting neuronal damage)

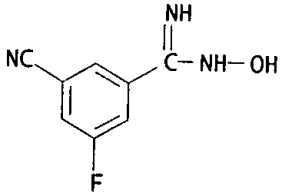
RN 453565-48-5 HCAPLUS
CN 2-Pyridinecarboximidamide, 5-cyano-N-hydroxy- (9CI) (CA INDEX NAME)



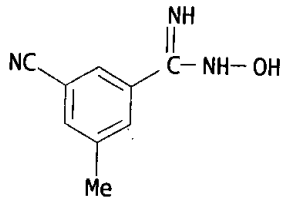
RN 453565-51-0 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy-5-methoxy- (9CI) (CA INDEX NAME)



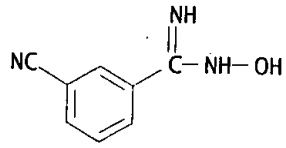
RN 453565-54-3 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-5-fluoro-N-hydroxy- (9CI) (CA INDEX NAME)



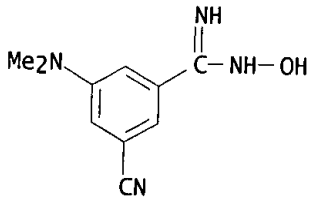
RN 453565-57-6 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



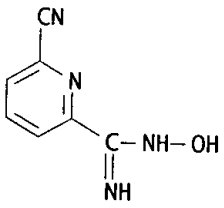
RN 453565-58-7 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy- (9CI) (CA INDEX NAME)



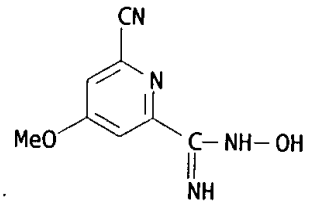
RN 453565-60-1 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-5-(dimethylamino)-N-hydroxy- (9CI) (CA INDEX NAME)



RN 453565-61-2 HCAPLUS
CN 2-Pyridinecarboximidamide, 6-cyano-N-hydroxy- (9CI) (CA INDEX NAME)

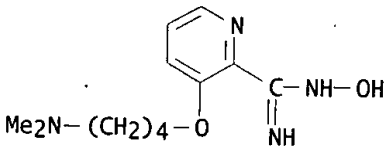


RN 453566-11-5 HCAPLUS
CN 2-Pyridinecarboximidamide, 6-cyano-N-hydroxy-4-methoxy- (9CI) (CA INDEX NAME)

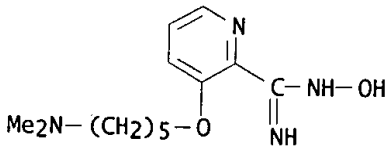


IT **453566-70-6**, 3-(4-Dimethylaminobutoxy)pyrid-2-ylamidoxime
453566-74-0, 3-(5-Dimethylaminopentyloxy)pyrid-2-ylamidoxime
453566-77-3, 3-(6-Dimethylaminohexyloxy)pyrid-2-ylamidoxime
453567-26-5, 3-Cyano-5-trifluoromethoxyphenylamidoxime
RL: RCT (Reactant); RACT (Reactant or reagent)
(precursor; prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor antagonists for inhibiting neuronal damage)

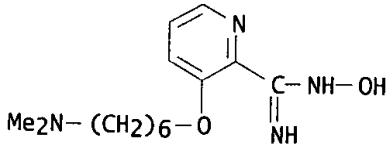
RN 453566-70-6 HCAPLUS
CN 2-Pyridinecarboximidamide, 3-[4-(dimethylamino)butoxy]-N-hydroxy- (9CI) (CA INDEX NAME)



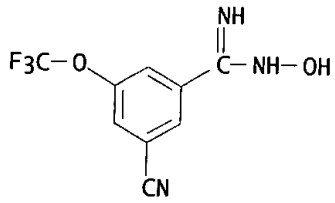
RN 453566-74-0 HCAPLUS
CN 2-Pyridinecarboximidamide, 3-[[5-(dimethylamino)pentyl]oxy]-N-hydroxy- (9CI) (CA INDEX NAME)



RN 453566-77-3 HCAPLUS
CN 2-Pyridinecarboximidamide, 3-[[6-(dimethylamino)hexyl]oxy]-N-hydroxy- (9CI) (CA INDEX NAME)



RN 453567-26-5 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy-5-(trifluoromethoxy)- (9CI) (CA INDEX NAME)

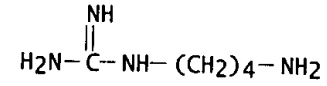


=> d ibib abs hitstr l60 2-38

L60 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:49216 HCAPLUS
TITLE: An in vivo evaluation of the **antiseizure** activity and acute neurotoxicity of agmatine
AUTHOR(S): Bence, Aimee K.; Worthen, David R.; Stables, James P.; Crooks, Peter A.
CORPORATE SOURCE: College of Pharmacy, Division of Pharmaceutical Sciences, University of Kentucky, Lexington, KY, 40536-0082, USA
SOURCE: Pharmacology, Biochemistry and Behavior (2003), 74(3), 771-775
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Agmatine, an endogenous cationic amine, exerts a wide range of biol. effects, including modulation of glutamate-activated N-methyl-d-aspartate (NMDA) receptor function in the central nervous system (CNS). Since glutamate and the NMDA receptor have been implicated in the initiation and spread of **seizure** activity, the capacity of agmatine to inhibit **seizure** spread was evaluated in vivo. Orally administered agmatine (30 mg/kg) protected against maximal electroshock **seizure** (MES)-induced **seizure** spread in rats as rapidly as 15 min and for as long as 6 h after administration. Inhibition of MES-induced **seizure** spread was also obsd. when agmatine was administered i.p. Agmatine's **antiseizure** activity did not appear to be dose-dependent. An in vivo neurotoxicity screen indicated that agmatine was devoid of any acute neurol. toxicity at the doses tested. These preliminary data suggest that agmatine has promising **anticonvulsant** activity.

IT **306-60-5**, Agmatine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antiseizure** activity and acute neurotoxicity of agmatine)
RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:5915 HCAPLUS
DOCUMENT NUMBER: 138:73081
TITLE: Preparation of nitrate esters of amino acids, hydroxyacids, and polyols as antiepileptics.
INVENTOR(S): Ongini, Ennio; Del Soldato, Piero
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000643	A1	20030103	WO 2002-EP6389	20020611

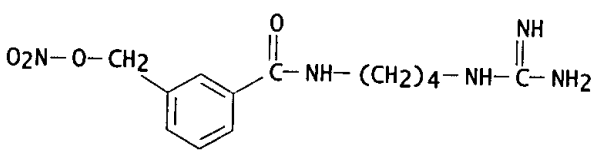
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TN, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 2001-MI1307 A 20010621
OTHER SOURCE(S): MARPAT 138:73081

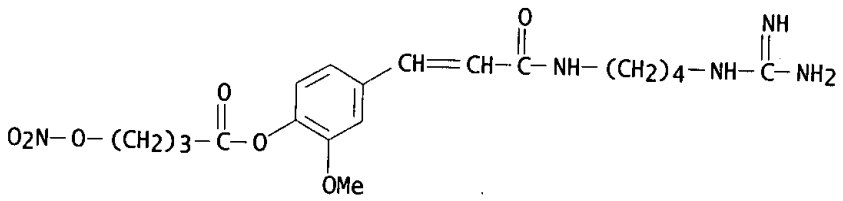
AB ABbDdNO2 [b, d = 0, 1; b, d cannot both = 0; A = RT1; R = R0R1R2W(CH2)m; W = C, N; m, n = 0-2; R0 = H, (CH2)nNHR1a; R1a = H, COR1h, CO2R1h; R1h = alkyl, Ph, PhCH2, etc.; R1 = H, electron pair; R2 = (substituted) Ph, PhCH2, amidino, etc.; B = TbX2Tbi; Tb = CO, X; Tbi = (CO)tx, Xtxx; tx, txx = 0, 1; X2 = bivalent radical; D = TcY; Tc = CO, X; Y = alkyleneoxy, cycloalkylene, [CH2CH(ONO2)CH2O]nf, (CH2)n3C6H4(CH2)n31O, etc.; nf = 1-6; n3 = 0-5; n31 = 1-3; with provisos], were prepd. as antiepileptics (no data). Thus, 1-(N-tert-butoxycarbonylaminomethyl)cyclohexaneacetic acid (prepn. given), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol (prepn. given), dicyclohexylcarbodiimide, and N,N-dimethylaminopyridine were stirred 3 h at room temp. in CHCl3/DMF to give 1-(N-tert-butoxycarbonylaminomethyl)cyclohexaneacetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester. This was stirred with HCl in EtOAc to give 1-(aminomethyl)cyclohexaneaceti c acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester hydrochloride.

IT **480464-76-4P 480464-77-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nitrate esters of amino acids, hydroxyacids, and polyols as **antiepileptics**)

RN 480464-76-4 HCAPLUS
CN Benzamide, N-[4-[(aminoiminomethyl)amino]butyl]-3-[(nitrooxy)methyl]- (9CI) (CA INDEX NAME)

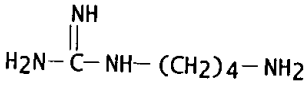


RN 480464-77-5 HCAPLUS
CN Butanoic acid, 4-(nitrooxy)-, 4-[3-[[4-[(aminoiminomethyl)amino]butyl]amino]-3-oxo-1-propenyl]-2-methoxyphenyl ester, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **306-60-5**, Agmatine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of nitrate esters of amino acids, hydroxyacids, and polyols as antiepileptics)
RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:676015 HCAPLUS
DOCUMENT NUMBER: 137:201315
TITLE: Heteropolycyclic compounds, particularly pyridyl- and phenyl-substituted 1,2,4-oxadiazoles and analogs, and their use as metabotropic glutamate receptor antagonists for inhibiting neuronal damage
INVENTOR(S): Slassi, Abdelmalik; Van Wagenen, Bradford; Stormann, Thomas M.; Moe, Scott T.; Sheehan, Susan M.; McLeod, Donald A.; Smith, Daryl L.; Isaac, Methvin Benjamin
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 272 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068417	A2	20020906	WO 2002-US4689	20020219
WO 2002068417	A3	20021114		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

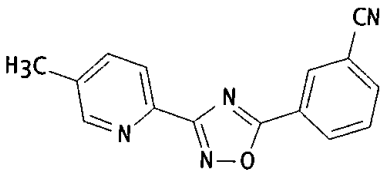
Searched by Susan Hanley 305-4053

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-269847P P 20010221

GI



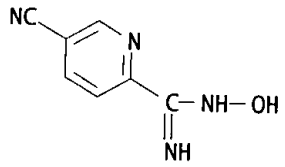
I

AB The invention provides compds. and pharmaceutical compns. that act as antagonists at metabotropic glutamate receptors, and that are useful for treating neurol. diseases and disorders. Methods of prepg. the compds. also are disclosed. The compds. exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, notably mGluR5. In particular, medical conditions assocd. with metabotropic glutamate receptors and therefore targeted by the invention compds. include stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, **epilepsy**, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease. The invention provides methods of treating diseases assocd. with excitatory activation of an mGluR Group I receptor, and of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, specifically wherein the mGluR Group I receptor is mGluR5. In one aspect of the invention, the antagonists may be represented by the general formula Ar1-L-Ar2, wherein Ar1 is an optionally substituted heteroarom. moiety, and Ar2 is an optionally substituted benzene ring. The L moiety is a group that not only covalently binds to the Ar1 and Ar2 moieties, and which facilitates adoption of the correct spatial orientation of Ar1 and Ar2, but also itself may interact with the protein, to effect receptor binding. In one embodiment of the invention, L is selected from the group consisting of -NH-, -S-, -O-, -CO-, -CONH-, -CONHCH2-, -CH2CONH-, -CNHNH-, -CNHNHCH2-, -C=NOCH2-, -CH2NHCH2-, -CH2CH2NH-, -NHCH2CO-, -NHCH2CHOH-, -NHCNHNH-, -NHCONH-, cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1H-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2H-pyran, 2H-pyran, 4H-pyran, tetrahydrothiopyran, 3,4-dihydro-2H-thiopyran, 2H-thiin, 4H-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine. In another embodiment of the invention, Ar1 is selected from the group consisting of Ph, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, and Ar2 is selected from the group

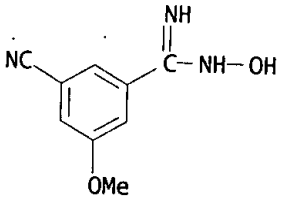
consisting of thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrroyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl. Several hundred specific examples are individually prepd. and/or claimed. A variety of intermediates were also prepd. For instance, 5-methylpyrid-2-ylamidoxime was prepd. from 2-bromo-5-methylpyridine by Zn- and Pd-complex-mediated cyanation (56%) and reaction of the resulting nitrile with NH2OH.HCl (60%). Cyclization of the amidoxime with 3-cyanobenzoyl chloride (86%) gave invention compd. I. In a bioassay for mGluR5 antagonism in primary astrocyte cultures from rats, the invention compds. had IC50 values in th range of 11 to 9140 nM.

IT **453565-48-5P**, 5-Cyanopyrid-2-ylamidoxime **453565-51-0P**, 3-Cyano-5-methoxyphenylamidoxime **453565-54-3P**, 3-Cyano-5-fluorophenylamidoxime **453565-57-6P**, 3-Cyano-5-methylphenylamidoxime **453565-58-7P**, 3-Cyanophenylamidoxime **453565-60-1P**, 3-Cyano-5-dimethylaminophenylamidoxime **453565-61-2P**, 6-Cyanopyrid-2-ylamidoxime **453566-11-5P**, 6-Cyano-4-methoxypyrid-2-ylamidoxime
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor antagonists for inhibiting neuronal damage)

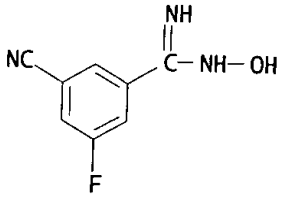
RN 453565-48-5 HCAPLUS
CN 2-Pyridinecarboximidamide, 5-cyano-N-hydroxy- (9CI) (CA INDEX NAME)



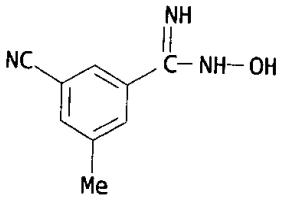
RN 453565-51-0 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy-5-methoxy- (9CI) (CA INDEX NAME)



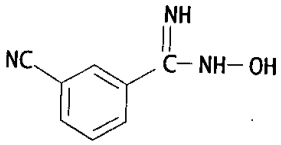
RN 453565-54-3 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-5-fluoro-N-hydroxy- (9CI) (CA INDEX NAME)



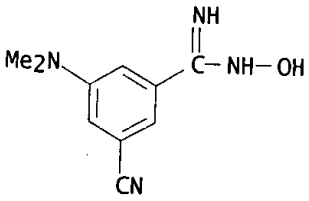
RN 453565-57-6 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



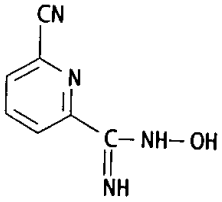
RN 453565-58-7 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-N-hydroxy- (9CI) (CA INDEX NAME)



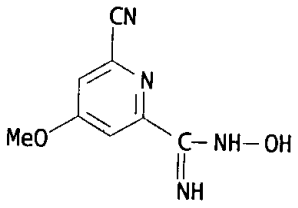
RN 453565-60-1 HCAPLUS
CN Benzenecarboximidamide, 3-cyano-5-(dimethylamino)-N-hydroxy- (9CI) (CA INDEX NAME)



RN 453565-61-2 HCAPLUS
CN 2-Pyridinecarboximidamide, 6-cyano-N-hydroxy- (9CI) (CA INDEX NAME)

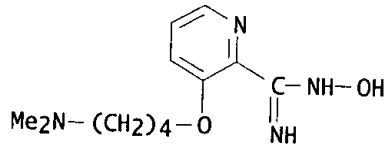


RN 453566-11-5 HCAPLUS
CN 2-Pyridinecarboximidamide, 6-cyano-N-hydroxy-4-methoxy- (9CI) (CA INDEX NAME)

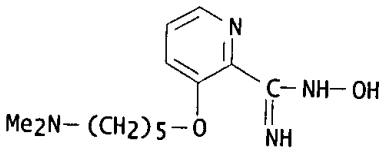


IT **453566-70-6**, 3-(4-Dimethylaminobutoxy)pyrid-2-ylamidoxime
453566-74-0, 3-(5-Dimethylaminopentyloxy)pyrid-2-ylamidoxime
453566-77-3, 3-(6-Dimethylaminohexyloxy)pyrid-2-ylamidoxime
453567-26-5, 3-Cyano-5-trifluoromethoxyphenylamidoxime
RL: RCT (Reactant); RACT (Reactant or reagent)
(precursor; prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor antagonists for inhibiting neuronal damage)

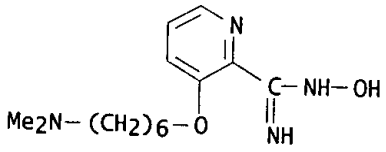
RN 453566-70-6 HCAPLUS
CN 2-Pyridinecarboximidamide, 3-[4-(dimethylamino)butoxy]-N-hydroxy- (9CI) (CA INDEX NAME)



RN 453566-74-0 HCAPLUS
CN 2-Pyridinecarboximidamide, 3-[[5-(dimethylamino)pentyl]oxy]-N-hydroxy- (9CI) (CA INDEX NAME)

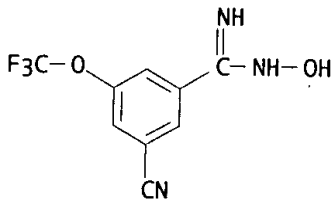


RN 453566-77-3 HCAPLUS
CN 2-Pyridinecarboximidamide, 3-[[6-(dimethylamino)hexyl]oxy]-N-hydroxy- (9CI) (CA INDEX NAME)



RN 453567-26-5 HCAPLUS

CN Benzenecarboximidamide, 3-cyano-N-hydroxy-5-(trifluoromethoxy)- (9CI) (CA INDEX NAME)



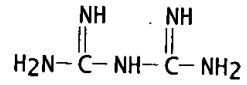
L60 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:637564 HCAPLUS
DOCUMENT NUMBER: 137:150247
TITLE: Combination therapy for type II diabetes and syndrome X using antidiabetic and anticonvulsant agents
INVENTOR(S): Connor, Gregory S.
PATENT ASSIGNEE(S): Ortho-Mcneil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002064210	A2	20020822	WO 2001-US50840	20011025
WO 2002064210	A3	20030306		

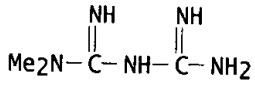
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002147157	A1	20021010	US 2001-42425	20011025

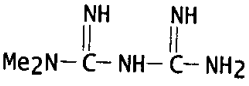
PRIORITY APPLN. INFO.: US 2000-244225P P 20001030
OTHER SOURCE(S): MARPAT 137:150247
AB The invention discloses a combination therapy comprising antidiabetic agents and anticonvulsant derivs. useful for the treatment of Type II diabetes mellitus and Syndrome X.
IT **56-03-1D**, Biguanide, derivs. **657-24-9**, Metformin **1115-70-4**, Metformin hydrochloride
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidiabetic-**anticonvulsant** agent combination therapy for type II diabetes and syndrome X)
RN 56-03-1 HCAPLUS
CN Imidodicarbonimidic diamide (9CI) (CA INDEX NAME)



RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 1115-70-4 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

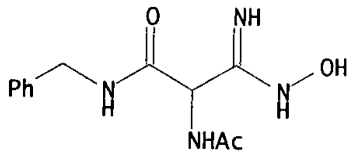
L60 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:402517 HCAPLUS
DOCUMENT NUMBER: 137:119061
TITLE: Quantitative Structure-Activity Relationship Analysis of Functionalized Amino Acid Anticonvulsant Agents Using k Nearest Neighbor and Simulated Annealing PLS Methods
AUTHOR(S): Shen, Min; LeTiran, Arnaud; Xiao, Yunde; Golbraikh, Alexander; Kohn, Harold; Tropsha, Alexander
CORPORATE SOURCE: Division of Medicinal Chemistry and Natural Products School of Pharmacy CB 7360, University of North Carolina, Chapel Hill, NC, 27599-7360, USA
SOURCE: Journal of Medicinal Chemistry (2002), 45(13), 2811-2823
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:119061

AB We report the development of rigorously validated quant. structure-activity relation (QSAR) models for 48 chem. diverse functionalized amino acids with anticonvulsant activity. Two variable selection approaches, simulated annealing partial least squares (SA-PLS) and k nearest neighbor (kNN), were employed. Both methods utilize multiple descriptors such as mol. connectivity indexes or atom pair descriptors, which are derived from two-dimensional mol. topol. QSAR models with high internal accuracy were generated, with leave-one-out cross-validated R2 (q2) values ranging between 0.6 and 0.8. The q2 values for the actual dataset were significantly higher than those obtained for the same dataset with randomly shuffled activity values, indicating that

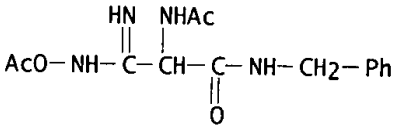
models were statistically significant. The original dataset was further divided into several training and test sets, with highly predictive models providing q2 values greater than 0.5 for the training sets and R2 values greater than 0.6 for the test sets. These models were capable of predicting with reasonable accuracy the activity of 13 novel compds. not included in the original dataset. The successful development of highly predictive QSAR models affords further design and discovery of novel anticonvulsant agents.

IT **147495-33-8 194732-96-2**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR anal. of functionalized amino acid **anticonvulsant** agents using k nearest neighbor and simulated annealing PLS methods)

RN 147495-33-8 HCAPLUS
CN Propanamide, 2-(acetylamino)-3-(hydroxyamino)-3-imino-N-(phenylmethyl)-(9CI) (CA INDEX NAME)



RN 194732-96-2 HCAPLUS
CN Propanamide, 2-(acetylamino)-3-[(acetyloxy)amino]-3-imino-N-(phenylmethyl)-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:923603 HCAPLUS
DOCUMENT NUMBER: 136:31716
TITLE: Agmatine and agmatine analogs in the treatment of **epilepsy**, **seizure**, and **electroconvulsive** disorders
INVENTOR(S): Crooks, Peter A.; Bence, Aimee K.; Worthen, David R.
PATENT ASSIGNEE(S): University of Kentucky Research Foundation, USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001095897	A1	20011220	WO 2001-US19095	20010615

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

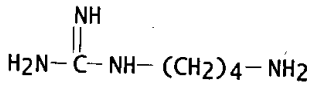
CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002065323 A1 20020530 US 2001-881215 20010615
PRIORITY APPLN. INFO.: US 2000-211532P P 20000615
OTHER SOURCE(S): MARPAT 136:31716

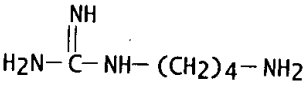
AB Pharmaceutical prepns. contg. of agmatine, congeners, analogs or derivs. thereof for use in preventing or treating **epilepsy**, **seizures**, and other **electroconvulsive** disorders, are provided. Embodiments include administering an effective amt. of agmatine, an agmatine analog or a pharmaceutically acceptable salt thereof to a human subject in need of treatment or prevention of **epilepsy**, **seizure** or other **electroconvulsive** disorder to treat, reduce, or prevent the disorder in the subject.

IT **306-60-5**, Agmatine **306-60-5D**, Agmatine, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agmatine and agmatine analogs for treatment of **epilepsy**, **seizure**, and **electroconvulsive** disorders)

RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

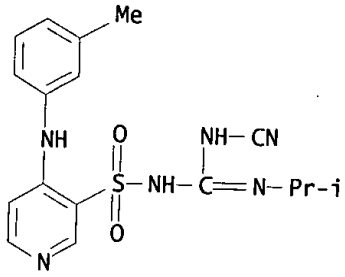
L60 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:892169 HCAPLUS
DOCUMENT NUMBER: 134:187827
TITLE: Isosterism among analogues of torasemide: conformational, electronic and lipophilic properties
AUTHOR(S): Wouters, Johan; Michaux, Catherine; Durant, Francois; Dogne, Jean Michel; Delarge, Jacques; Masereel, Bernard
CORPORATE SOURCE: Laboratory of Molecular Structure and Department of Pharmacy, Facultes Universitaires Notre Dame de la Paix, Namur, B-5000, Belg.
SOURCE: European Journal of Medicinal Chemistry (2000), 35(10), 923-929
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Editions Scientifiques et Medicales Elsevier

DOCUMENT TYPE: Journal
LANGUAGE: English

AB The structures, electronic (charges, mol. electrostatic potential, MOs) and lipophilic properties of three isostere analogs of torasemide were detd. and the influence of the replacement of the sulfonyl urea group on the conformation and electronic properties of the mols. is discussed. Lipophilicity of the compds. seems to be the most discriminating property along the series and affects their pharmacol. activities (diuretic and anticonvulsant).

IT **162586-76-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isosterism among analogs of torasemide and conformational and electronic and lipophilic properties in relation to pharmacol. activities as diuretics and **anticonvulsants**)

RN 162586-76-7 HCAPLUS
CN 3-Pyridinesulfonamide, N-[(cyanoamino)[(1-methylethyl)amino]methylene]-4-[(3-methylphenyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:725417 HCAPLUS
DOCUMENT NUMBER: 133:276363
TITLE: Association of NO-synthase inhibitors and metabolic antioxidants
INVENTOR(S): Auguet, Michel; Harnett, Jeremiah; Chabrier De Lassauniere, Pierre-etienne
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S, Fr.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059448	A2	20001012	WO 2000-FR812	20000331
WO 2000059448	A3	20010308		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,

SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

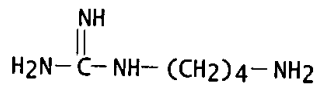
FR 2791571	A1	20001006	FR 1999-4134	19990402
FR 2791571	B1	20021004		
EP 1169005	A2	20020109	EP 2000-915262	20000331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001004770	A	20011123	NO 2001-4770	20011001

PRIORITY APPLN. INFO.: FR 1999-4134 A 19990402
WO 2000-FR812 W 20000331

AB The invention relates to a pharmaceutical compn. comprising as an active ingredient one or several substances interfering with the synthesis of nitrogen monoxide by inhibiting NO-synthase and one or several metabolic antioxidants contg. thiol groups and intervening in the redox status of the thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product contg. one or several NO-synthase inhibitors and one or several metabolic antioxidants intervening in the redox status of the thiol groups, as a combined product in a sepd. form of said active ingredients. A mixt. of 3 mg/kg N-phenyl-2-thiophenecarboximidamine and 10 mg/kg lipoic acid increased the dopamine level in guinea pigs suffering from parkinson to 5.21 ng/mg nervous tissue which was higher than either compds.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(assocn. of NO-synthase inhibitors and metabolic antioxidants)

RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



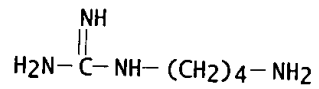
L60 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:762300 HCAPLUS
DOCUMENT NUMBER: 132:202985
TITLE: Effects of agmatine on ethanol withdrawal syndrome in rats
AUTHOR(S): Uzbay, I. T.; Yesilyurt, O.; Celik, T.; Ergun, H.; Isimer, A.
CORPORATE SOURCE: Faculty of Medicine, Psychopharmacology Research Unit, Department of Medical Pharmacology, Gulhane Military Medical Academy, Etlik, Ankara, 06018, Turk.
SOURCE: Behavioural Brain Research (2000), 107(1,2), 153-159
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Effects of agmatine, which is an endogenous polyamine metabolite formed by decarboxylation of L-arginine, have been investigated on the ethanol withdrawal syndrome in rats. Adult male Wistar rats were used in the study. Ethanol (7.2% vol./vol.) was given to the rats by a liq. diet for 21 days. Agmatine (20, 40, 80 and 160 mg/kg) and saline were injected to

rats i.p. 30 min before ethanol withdrawal testing. After 30th min, 2nd and 6th h of ethanol withdrawal, rats were obsd. for 5 min, and withdrawal signs which included locomotor hyperactivity, agitation, stereotyped behavior, wet dog shakes and tremor were recorded or rated. A second series of injections was given at 6 h after the first one, and subjects were then tested for audiogenic **seizures**. Agmatine caused dose-dependent and significant inhibitory effects on stereotyped behaviors, wet dog shakes and tremors during the observation period. It did not cause any significant change in motor coordination of naive (not ethanol-dependent) rats. The authors' results suggest that agmatine attenuates withdrawal syndrome in ethanol-dependent rats; thus, this drug may be beneficial in the treatment of ethanol dependence.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agmatine effects on ethanol withdrawal syndrome in rats)

RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:272160 HCAPLUS
DOCUMENT NUMBER: 130:307014
TITLE: Histamine H2-receptor modulation in two mouse models of seizure susceptibility
AUTHOR(S): Seeley, N. A.; Sturman, G.; Meade, H. M.
CORPORATE SOURCE: Dep. Life Sci., Univ. East London, London, E15 4LZ, UK
SOURCE: Inflammation Research (1999), 48(Suppl. 1), S67-S68
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

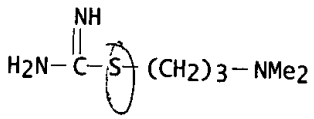
AB Using dimaprit and zolantidine, histamine H2-receptor modulation was evaluated in 2 mouse seizure models (seizure chem. induced with leptazol and the DBA/2 mouse strain). Dimaprit (0.3-3 mg/kg) produced a dose-related decrease in the leptazol-seizure model in male BK/TO mice with anticonvulsant effects at 0.3, 1, and 3.0 mg/kg in the occurrence of seizure incidence. The severity of the seizures was also dose-related reduced. In female BK/TO mice, dimaprit (1 mg/kg) increased the leptazol dose needed to evoke tonic seizures by .apprx.50%, whereas zolantidine (10 mg/kg) reduced the amt. of leptazol needed to evoke clonic seizure in female CD1 mice by >10%. In audiogenic susceptible mice, dimaprit (0.2-3 mg/kg) reduced the seizure score of 3.20 in the controls to 2.25, reduced the wild running in the mice, and a difference in respiratory arrest was seen at 1 mg/kg. Zolantidine (3 and 10 mg/kg) increased the seizure score of 3.12 in the controls to 4.0. It is concluded that histamine H2-receptor has a modulatory role in epileptic induced seizures in mice.

IT **65119-89-3**, Dimaprit
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**anticonvulsive** activities of dimaprit in mouse models of **seizure** susceptibility)

RN 65119-89-3 HCAPLUS

CN Carbamimidothioic acid, 3-(dimethylamino)propyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:169475 HCAPLUS

DOCUMENT NUMBER: 128:248580

TITLE: Association of NO synthase inhibitors with trappers of reactive oxygen species

INVENTOR(S): Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis

PATENT ASSIGNEE(S): Societe De Conseils De Recherches Et D'applications Scientifiques (S.C.R.A.S, Fr.; Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis

SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9809653	A1	19980312	WO 1997-FR1567	19970905
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2753098	A1	19980313	FR 1996-10875	19960906
FR 2753098	B1	19981127		
AU 9742111	A1	19980326	AU 1997-42111	19970905
AU 734296	B2	20010607		
EP 939654	A1	19990908	EP 1997-940183	19970905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 334597	A	20001027	NZ 1997-334597	19970905
JP 2000517336	T2	20001226	JP 1998-512314	19970905
RU 2174844	C2	20011020	RU 1999-106792	19970905
US 6297281	B1	20011002	US 1999-254254	19990302
NO 9901100	A	19990505	NO 1999-1100	19990305

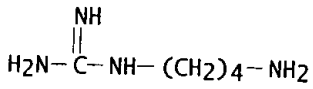
PRIORITY APPLN. INFO.:
FR 1996-10875 A 19960906
WO 1997-FR1567 W 19970905

AB The invention concerns a pharmaceutical compn. contg., as active principle, at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance, optionally with a pharmaceutically acceptable support. The invention also concerns a product contg. at least

one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance as combined product of these active principles in sep. form.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(assocn. of NO synthase inhibitors with trappers of reactive oxygen species)

RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:613818 HCAPLUS
DOCUMENT NUMBER: 127:205889
TITLE: Preparation of amino acid derivatives as anticonvulsants
INVENTOR(S): Kohn, Harold L.; Watson, Darrell
PATENT ASSIGNEE(S): Research Corporation Technologies, Inc., USA
SOURCE: U.S., 49 pp., Cont.-in-part of U.S. 5,378,729.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

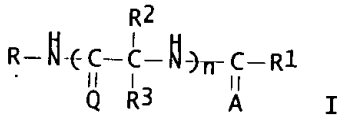
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5654301	A	19970805	US 1993-3208	19930112
AU 595538	B2	19900405	AU 1986-61766	19860821
AU 8661766	A1	19880225		
AU 609062	B2	19910426	AU 1987-79491	19871006
AU 8779491	A1	19890406		
JP 03506045	T2	19911226	JP 1990-508758	19900518
US 5378729	A	19950103	US 1991-710610	19910604
WO 9221648	A1	19921210	WO 1992-US4687	19920604

W: AU, CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE

PRIORITY APPLN. INFO.:

US 1985-702195	A2	19850215
US 1986-916254	A2	19861007
US 1987-80528	B2	19870731
US 1989-354057	B2	19890519
US 1989-392870	B2	19890811
US 1991-710610	A2	19910604
WO 1992-US4687	W	19920604
WO 1990-US2834	W	19900518

OTHER SOURCE(S): MARPAT 127:205889
GI

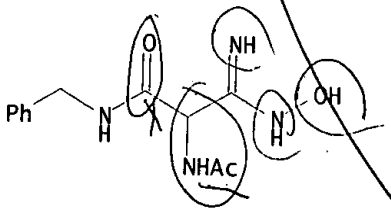


I

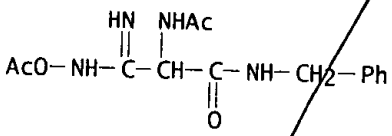
AB Amino acid derivs. I [R = H, (un)substituted lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl; R1 = H, (un)substituted lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl; R2, R3 = independently R, SO3-, Z-Y; Z = O, S, S(O)a, NR4, PR4, bond; Y = H, (un)substituted lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, heterocyclic lower alkyl, cycloalkyl, cycloalkyl lower alkyl; Z-Y = NR4 NR5R7, NR4OR5, ONR4R7, OPR4R5, PR4OR5, SNR4R7, NR4SR7, SPR4R5, PR4SR7, NR4PR5R6PR4NR5R7; NR4COR5, SCOR5, NR4CO2R5, SCO2R5, NR4CONR4R5, NR4CONR5S(O)aR6, NR4CSNR5R6, NR4C(Q)MNR5C(A)OR6, CSNH2; R4-R6 = independently H, (un)substituted lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl; R7 = R6, CO2R8, COR8; R8 = H, (un)substituted lower alkyl, aryl lower alkyl; A, Q = independently O, S; M = (CH2)m, bond; m = 1-6; n = 1-4; a = 1-3] are claimed as anticonvulsants. Thus, acetylation of H-DL-Ala-NHCH2Ph with Ac2O in CH2Cl2 gave 54% Ac-DL-Ala-NHCH2Ph (II). II and related N-acetylamino acid benzylamides were tested for anticonvulsant activity in mice.

IT **147495-33-8P 194732-96-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of amino acid derivs. as **anticonvulsants**)

RN 147495-33-8 HCAPLUS
CN Propanamide, 2-(acetylamino)-3-(hydroxyamino)-3-imino-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 194732-96-2 HCAPLUS
CN Propanamide, 2-(acetylamino)-3-[(acetyloxy)amino]-3-imino-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



L60 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:600815 HCAPLUS
DOCUMENT NUMBER: 127:272247

TITLE: Pharmacomodulation of torasemide led to original diuretic, neuroprotective, anticonvulsant and antithrombotic drugs

AUTHOR(S): Masereel, B.; Dogne, J. M.; Damas, J.; Nuhrich, A.; Varache-Lembege, M.; Fontaine, J.; Pochet, L.; Somers, F.; de Tullio, P.; Pirotte, B.; Delarge, J.

CORPORATE SOURCE: Dep. Medicinal Chem., Univ. Liege, Liege, B-4000, Belg.

SOURCE: Journal de Pharmacie de Belgique (1997), 52(4), 157-158
CODEN: JPBEAJ; ISSN: 0047-2166

PUBLISHER: Masson

DOCUMENT TYPE: Journal

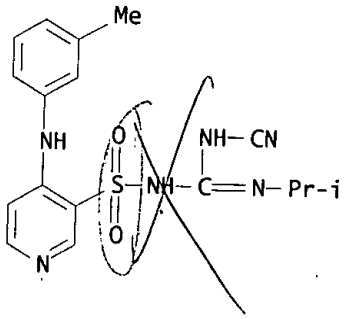
LANGUAGE: English

AB Pharmacomodulation of torasemide, a diuretic sulfonylurea, led to the discovery of two novel diuretics, a sulfonylthiourea (BM 20) and a sulfonylcyanoguanidine (BM 106). BM 27, a lipophilic sulfonylurea, exhibited neuroprotective properties assocd. to an anticonvulsant activity. As BM 27, two lipophilic sulfonylthioureas (BM 11 and BM 34) revealed an anticonvulsant profile similar to that of phenytoin. Finally the synthesis of torasemide derivs. led to the development of a sulfonylcyanoguanidine (BM 144) with a thromboxane A2 antagonist potency.

IT **162586-76-7**, BM 106
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacomodulation of torasemide led to original diuretic, neuroprotective, **anticonvulsant** and antithrombotic drugs)

RN 162586-76-7 HCAPLUS

CN 3-Pyridinesulfonamide, N-[(cyanoamino)[(1-methylethyl)amino]methylene]-4-[(3-methylphenyl)amino]- (9CI) (CA INDEX NAME)



L60 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:376495 HCAPLUS

DOCUMENT NUMBER: 127:93671

TITLE: Effects of the 5-HT3 receptor agonist 1-(m-chlorophenyl)-biguanide in the rat kindling model of epilepsy

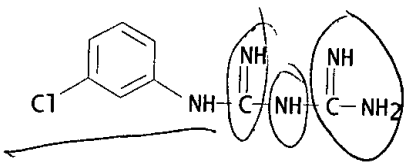
AUTHOR(S): Wada, Yuji; Shiraishi, Jun; Nakamura, Mitsuhiko; Koshino, Yoshifumi

CORPORATE SOURCE: Department of Neuropsychiatry, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa, 920, Japan

SOURCE: Brain Research (1997), 759(2), 313-316
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study assessed the action of the serotonin3 (5-HT3) receptor agonist, 1-(m-chlorophenyl)-biguanide (m-CPBG), against both kindled seizures and kindling development from the rat amygdala (AM). The intracerebroventricular (i.c.v.) administration of 40 .mu.g m-CPBG significantly increased the duration of afterdischarge and bilateral forelimb clonus of generalized kindled seizures. In addn., daily i.c.v. treatment with m-CPBG at the same dose prior to each elec. stimulation to the AM significantly facilitated behavioral and electrog. seizure development and reduced the no. of stimulations needed to elicit generalized seizures. The present results indicate that m-CPBG increases the duration of fully kindled seizures and facilitates the developmental seizure process, suggesting an excitatory role of 5-HT3 receptors in the kindling model of epilepsy.
IT **92503-73-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
RN 92503-73-6 HCAPLUS
CN Imidodicarbonimidic diamide, N-(3-chlorophenyl)-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

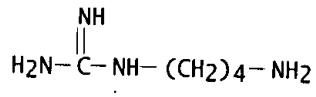
L60 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:430360 HCAPLUS
DOCUMENT NUMBER: 125:137120
TITLE: Quantitation of the putative neurotransmitter agmatine as the hexafluoroacetylacetonate derivative by stable isotope dilution gas chromatography and negative-ion chemical ionization mass spectrometry
AUTHOR(S): Stickle, Douglas; Bohrer, Alan; Berger, Richard; Morrissey, Jeremiah; Klahr, Saulo; Turk, John
CORPORATE SOURCE: Mass Spectrometry Resource Div. Lab. Med., Washington Univ. Sch. Med., St. Louis, MO, 63110, USA
SOURCE: Analytical Biochemistry (1996), 238(2), 129-136
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A method is described for detection and quantitation of agmatine [4-(aminobutyl)guanidine] by gas chromatog./neg.-ion chem.-ionization/mass spectrometry after derivatization with hexafluoroacetylacetone. The lower limit of detection of the deriv. was about 25 fmol on-column. For quant. studies of agmatine content in biol. samples, a procedure utilizing an internal std. ([15N4]agmatine prepd. from [15N4]arginine) and an extn. step had a lower limit of detection of about 15 pmol for total sample content. Agmatine content was measured in rat tissue samples and

normalized to protein content. Kidney and spleen samples exhibited the greatest content of agmatine per unit protein mass but agmatine was also detected in pancreatic islets and brain regions (cerebellum and cerebral cortex). On the basis of these measurements, it is estd. that the pancreatic islet intracellular agmatine concn. may exceed 1 .mu.M. The sensitive and highly specific means of detection and quantitation provided by mass spectrometry may be useful in investigating the physiol. role of agmatine in mammalian systems.

IT **306-60-5DP**, Agmatine, hexafluoroacetylacetone conjugates
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(putative neurotransmitter agmatine detn. as hexafluoroacetylacetonate deriv. by gas chromatog./ mass spectrometry)

RN 306-60-5 HCAPLUS

CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



L60 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:206613 HCAPLUS

DOCUMENT NUMBER: 122:6277

TITLE: Structure-activity relationships of arginine analogs on nitric oxide synthase activity in the rat brain

AUTHOR(S): Yokoi, I.; Kabuto, H.; Habu, H.; Inada, K.; Toma, J.; Mori, A.

CORPORATE SOURCE: Inst. Mol. Cellular Medicine, Okayama Univ. Med. School, Okayama, 700, Japan

SOURCE: Neuropharmacology (1994), 33(11), 1261-5
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

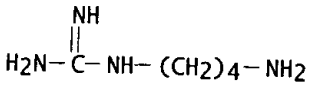
LANGUAGE: English

AB Nitric oxide (NO) is synthesized by nitric oxide synthase (NOS) from L-arginine (Arg) which as a guanidino group in its mol. We examd. the effect of 23 different Arg analogs on NOS activity in the rat brain. Though homoarginine, .epsilon.-guanidinocaproic acid and canavanine act as substrates of NOS, prodn. of NO from them was lower than that from Arg. .alpha.-Guanidinoglutaric acid (2-GGA) and arcaine inhibited NOS activity at levels equal to NG-monomethyl-L-arginine (MeArg), a well known NOS inhibitor. Though almost all previously reported NOS inhibitors were synthesized by substituting the guanidino nitrogen of Arg, the guanidino nitrogens of arcaine and 2-GGA were not substituted. Furthermore, 2-GGA is a known endogenous **convulsant** in mammals, and arcaine, which was isolated from a marine mollusc, is also a **convulsive** substance. Hence, 2-GGA and arcaine will be excellent drugs to investigate not only the chem. nature of NOS but also the physiol. function of NO.

IT **306-60-5**, Agmatine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationships of arginine analogs on nitric oxide synthase activity in brain)

RN 306-60-5 HCAPLUS

CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)

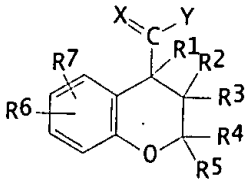


L60 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:407803 HCAPLUS
DOCUMENT NUMBER: 117:7803
TITLE: Preparation of benzopyran derivatives as potassium channel activators
INVENTOR(S): Koga, Hiroshi; Nabata, Hiroyuki
PATENT ASSIGNEE(S): Chugai Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9202514	A1	19920220	WO 1991-JP1005	19910726
W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2087859	AA	19920128	CA 1991-2087859	19910726
CA 2087859	C	20020101		
AU 9182308	A1	19920302	AU 1991-82308	19910726
ZA 9105891	A	19921028	ZA 1991-5891	19910726
EP 541807	A1	19930519	EP 1991-913311	19910726
EP 541807	B1	19971217		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 161254	E	19980115	AT 1991-913311	19910726
ES 2111572	T3	19980316	ES 1991-913311	19910726
JP 3210665	B2	20010917	JP 1991-512381	19910726
US 5412117	A	19950502	US 1993-962215	19930126

PRIORITY APPLN. INFO.: JP 1990-199738 A 19900727
JP 1990-297009 A 19901101
JP 1991-49827 A 19910314
WO 1991-JP1005 A 19910726

OTHER SOURCE(S): MARPAT 117:7803
GI



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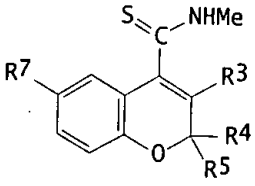


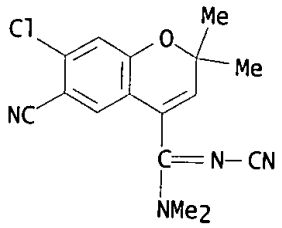
II

AB The title compds. [I; X = O, S, NZ, CHNO2; Z = H, alkyl, aryl, OH, alkoxy, cyano, carbamoyl, sulfamoyl; Y = NR8R9, OR10, SR11; R8, R9 = H, OH, alkoxy, cyano, (un)substituted amino, -cycloalkyl, -heteroaryl, -

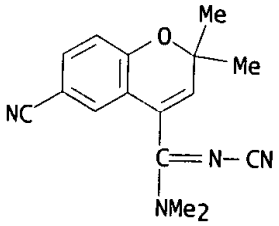
(un)satd. alkyl; or NR8R9 = (un)substituted heterocyclyl; R1, R10, R11 = H, alkyl, aryl; or R1R2 = bond; R2, R3 = H, OH; or R2R3 = O; R4, R5 = H, alkyl; or R4R5 = polymethine; R6, R7 = H, (halo)alkyl, halo, (halo)alkoxy, amino, acylamino, NO2, cyano, ester, alkyl-, or arylsulfonyl; or R6R7 = NON], useful for treatment of, e.g., asthma and **epilepsy**, are prepd. Thus, 0.93g tert-BuOK was added to a stirred mixt. of 1.5g 6-cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-one and MeNCS in DMF under ice-cooling and the mixt. was stirred for 4 h under ice-cooling to give a title compd. (II; R3 = OH, R4 = R5 = Me, R7 = cyano). II (R3 = H, R4 = R5 = Et, R7 = NO2) in vitro inhibited aminophylline-induced contraction of a rat's aorta and a guinea pig's tracheal muscle with IC50 of 3.7 .times. 10-11 and 5.0 .times. 10-8, resp. A total of 284 I were prepd.

IT **141570-76-5P 141570-77-6P 141571-75-7P 141571-81-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as potassium channel activator)

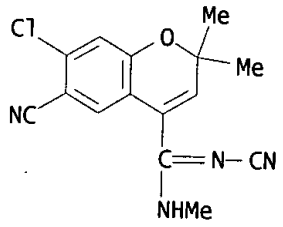
RN 141570-76-5 HCAPLUS
CN 2H-1-Benzopyran-4-carboximidamide, 7-chloro-N',6-dicyano-N,N,2,2-tetramethyl- (9CI) (CA INDEX NAME)



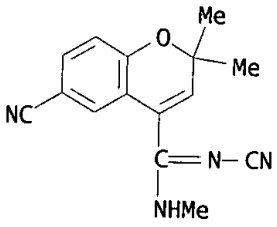
RN 141570-77-6 HCAPLUS
CN 2H-1-Benzopyran-4-carboximidamide, N',6-dicyano-N,N,2,2-tetramethyl- (9CI) (CA INDEX NAME)



RN 141571-75-7 HCAPLUS
CN 2H-1-Benzopyran-4-carboximidamide, 7-chloro-N,6-dicyano-N',2,2-trimethyl- (9CI) (CA INDEX NAME)



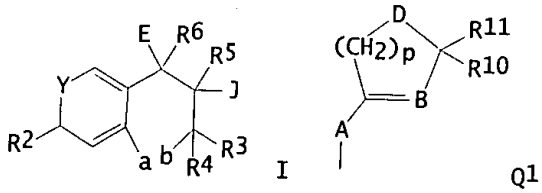
RN 141571-81-5 HCAPLUS
CN 2H-1-Benzopyran-4-carboximidamide, N,6-dicyano-N',2,2-trimethyl- (9CI) (CA INDEX NAME)



L60 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:95171 HCAPLUS
DOCUMENT NUMBER: 114:95171
TITLE: Use of benzopyran derivatives in the treatment of **epilepsy**
INVENTOR(S): Hamilton, Thomas Conway
PATENT ASSIGNEE(S): Beecham Group PLC, UK
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 372998	A2	19900613	EP 1989-312839	19891208
EP 372998	A3	19910717		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2004777	AA	19900608	CA 1989-2004777	19891206
DK 8906154	A	19900609	DK 1989-6154	19891206
ZA 8909304	A	19910424	ZA 1989-9304	19891206
AU 8946032	A1	19900621	AU 1989-46032	19891207
JP 02212426	A2	19900823	JP 1989-318698	19891207
JP 2791810	B2	19980827		

PRIORITY APPLN. INFO.: GB 1988-28679 19881208
OTHER SOURCE(S): MARPAT 114:95171
GI



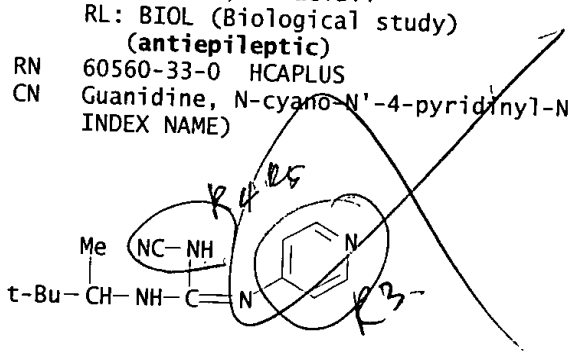
I Q1

AB A K channel activator is used in the manuf. of a medicament for the treatment of **epilepsy**. The activator is pinacidil or benzopyran deriv. I [a and b = O or bond or CH2 when E = Q and J = H; Q = R8NC(:X)R7; Y = N and R2 = H or Y = CR1; R1, R2 = H, NO2, CN, halo, CF3, formyl, etc.; or R1 and R2 form 2,1,3-oxadiazole; R3, R4 = H, C1-4 alkyl; or R3 and R4 = C2-5 polymethylene; R5 = H, OH, C1-6 alkoxy, C1-7 acyloxy, ONO2; R6 = H, or R5 and R6 = bond; J = H, C1-6 alkyl; E = Q, Q1, etc.; X = O, S, etc.; R7 = H, C1-6 alkyl, C1-6 alkoxy, etc.; R8 = H, C1-6 alkyl, ORP, NHCORq; or R7 and R8 form C3-4 polymethylene etc.; Rp = H, C1-6 alkyl, aralkyl, C1-7 alkanoyl, aroyl, Rq = R7; A = O, NR12; B = N, CR13; D = CH2, O, S, etc.; p = 1-3; R10, R11 = H, Me; or R10 and R11 = O, S; R12 = H, C1-4 alkyl, formyl, acetyl, hydroxymethyl; R13 = H, halo, formyl, hydroxymethyl; the E group is trans to R5]. Complete or almost complete prevention of MCD (most cell degranulating peptide of bee venom)-induced **seizures** was obsd. after a previous injection of BRL 38227 (10 and 100 nmol).

IT **60560-33-0**, Pinacidil
RL: BIOL (Biological study)
(antiepileptic)

RN 60560-33-0 HCAPLUS

CN Guanidine, N-cyano-N'-4-pyridinyl-N''-(1,2,2-trimethylpropyl)- (9CI) (CA INDEX NAME)



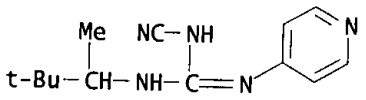
L60 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:511 HCAPLUS
DOCUMENT NUMBER: 114:511
TITLE: Effects of potassium channel openers on pentylenetetrazole-induced seizures in mice
AUTHOR(S): Del Pozo, Esperanza; Barrios, Manuel; Baeyens, Jose M.
CORPORATE SOURCE: Med. Sch., Granada Univ., Granada, 18012, Spain
SOURCE: Pharmacology & Toxicology (Oxford, United Kingdom) (1990), 67(2), 182-4
CODEN: PHTOEH; ISSN: 0901-9928
DOCUMENT TYPE: Journal
LANGUAGE: English

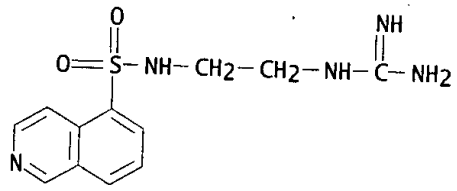
AB The effects of two K+ channel openers, cromakalim and pinacidil, on pentylenetetrazole-induced seizures were studied in mice. Cromakalim, but not pinacidil, dose-dependently inhibited convulsions. The mechanism of this anticonvulsant effect probably involves the opening of K+ channels, since it was completely reversed by 4-aminopyridine.

IT **60560-33-0**, Pinacidil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

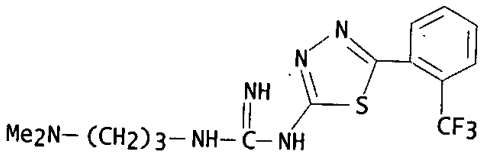
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**anticonvulsant** activity of, potassium channels in)
RN 60560-33-0 HCAPLUS
CN Guanidine, N-cyano-N'-4-pyridinyl-N''-(1,2,2-trimethylpropyl)- (9CI) (CA INDEX NAME)



L60 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:526531 HCAPLUS
DOCUMENT NUMBER: 113:126531
TITLE: Anticonvulsant properties of some calcium antagonists on sound-induced seizures in genetically epilepsy prone rats
AUTHOR(S): De Sarro, Giovambattista; De Sarro, Angelina; Federico, Francesco; Meldrum, Brian S.
CORPORATE SOURCE: Fac. Med., Univ. Messina, Messina, 98100, Italy
SOURCE: General Pharmacology (1990), 21(5), 769-78
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The anticonvulsant activity of calcium channel antagonists, was studied after i.p. or oral administration in genetically epilepsy prone rats (GEPR). Flunarizine, dihydropyridines and HA 1004, administered i.p., were the most potent compds. Diltiazem, prenylamine, perhexiline, verapamil and methoxyverapamil, given i.p., were able to reduce the incidence of the tonic phase but were completely ineffective in preventing clonic and running phases of sound-induced seizures in GEPR. Similar anticonvulsant activity was obsd. when these compds. were administered orally. After intracerebroventricular administration of some of the hydrosol. calcium antagonists studied, the anticonvulsant effects were similar to those obsd. after systemic administration. The systemic administration of Bay K 8644, a dihydropyridine analog, having the ability to stimulate calcium entry into cells produced a dose-dependent increase in clonic and tonic convulsions and other epileptic phenomena, which were prevented by pretreatment with nimodipine or nitrendipine. The possible role of purinergic, excitatory amino acid, GABA-benzodiapine mechanisms as well as the role of Ca2+-calmodulin and calcium channel binding sites on the anticonvulsant effects of some calcium antagonists are discussed.
IT **91742-10-8**, HA 1004
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**anticonvulsant** activity of, mechanism of)
RN 91742-10-8 HCAPLUS
CN 5-Isoquinolinesulfonamide, N-[2-[(aminoiminomethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



L60 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:98469 HCAPLUS
DOCUMENT NUMBER: 112:98469
TITLE: Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 3. Guanidines [Erratum to document cited in CA106(19):156365r]
AUTHOR(S): Chapleo, Christopher B.; Myers, Peter L.; Smith, Alan C. B.; Tulloch, Ian F.; Turner, Stephen; Walter, Donald S.
CORPORATE SOURCE: Dep. Med. Chem., Reckitt and Colman PLC, Hull, HU8 7DS, UK
SOURCE: Journal of Medicinal Chemistry (1989), 32(12), 2582
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An author mass omitted from the original article has been added. The error was reflected in the abstr. and index entries.
IT **107114-87-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **anticonvulsant** activity of (Erratum))
RN 107114-87-4 HCAPLUS
CN Guanidine, N-[3-(dimethylamino)propyl]-N'-[5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl]- (9CI) (CA INDEX NAME)

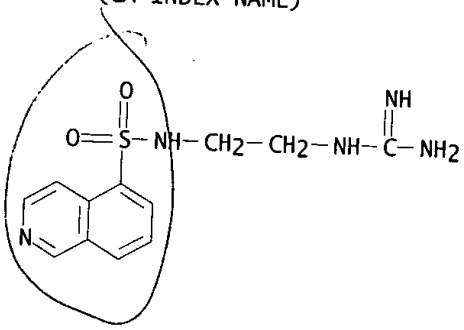


L60 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:106370 HCAPLUS
DOCUMENT NUMBER: 108:106370
TITLE: Anticonvulsant effects of some calcium entry blockers in DBA/2 mice
AUTHOR(S): De Sarro, G. B.; Meldrum, B. S.; Nistico, G.
CORPORATE SOURCE: Fac. Med., Univ. Reggio Calabria, Italy
SOURCE: British Journal of Pharmacology (1988), 93(2), 247-56
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The behavioral and anticonvulsant effects of several drugs acting by various mechanisms on Ca-channels or affecting intracellular Ca2+ concns.

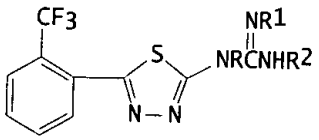
were studied after both systemic and intracerebroventricular administration in DBA/2 mice, a strain genetically susceptible to sound-induced seizures. The anticonvulsant effects were evaluated on seizures evoked by means of auditory stimulation in animals placed singly under a perspex dome. Flunarizine and dihydropyridine derivs., belonging to class I of Ca entry blockers, administered i.p., were the most potent compds. Diltiazem, a benzothiazepine deriv. belonging to class III, and HA 1004, a Ca antagonist, acting by inhibiting Ca mobilization from intracellular stores, injected i.p., were 3-7.6-fold and 5.8-10.7-fold less potent than flunarizine, resp. Verapamil and methoxyverapamil, 2 phenylalkylamine derivs., given i.p., were completely ineffective in preventing sound-induced seizures in DBA/2 mice. In addn., high doses of verapamil and its methoxy deriv. occasionally produced spontaneous tonic-clonic seizures. After intracerebroventricular administration of the Ca entry blockers, belonging to different classes, the anticonvulsant effects were similar to those obsd. after systemic administration. The systemic administration of Bay K 8644, a dihydropyridine analog, having the ability to stimulate Ca entry into cells produced a dose-dependent increase in clonic and tonic convulsions and other neurol. side effects. Thus, Ca antagonists may be useful in human epilepsy.

IT **91742-10-8**, HA 1004
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**anticonvulsant** activity of)

RN 91742-10-8 HCAPLUS
CN 5-Isoquinolinesulfonamide, N-[2-[(aminoiminomethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



L60 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:156365 HCAPLUS
DOCUMENT NUMBER: 106:156365
TITLE: Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 3. Guanidines
AUTHOR(S): Chapleo, Christopher B.; Myers, Peter L.; Smith, Alan C. B.; Tulloch, Ian F.; Walter, Donald S.
CORPORATE SOURCE: Dep. Med. Chem., Reckitt and Colman PLC, Hull, HU8 7DS, UK
SOURCE: Journal of Medicinal Chemistry (1987), 30(5), 951-4
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 106:156365
GI



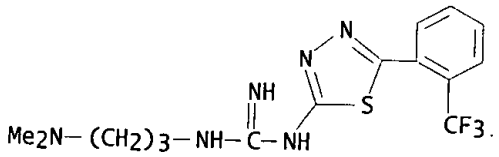
I

AB The synthesis and anticonvulsant activity of aryl(guanidino)thiadiazoles I [R = H, Me; R1 = H, R2 = H, alkyl, PhCH2, etc.; R1R2 = (CH2)2, Me2CCH2] are described. The unsubstituted guanidine I [R-R2 = H (II)] was found to possess potent anticonvulsant properties; considerable redn. or loss of activity, however, was obsd. with the majority of the substituted guanidines. Incorporation of the guanidine group into an imidazoline ring also resulted in a loss of activity. Secondary pharmacol. evaluation confirmed the anticonvulsant properties of II, but also revealed that the compd. exhibited a considerable degree of sedative activity.

IT **107114-87-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **anticonvulsant** activity of)

RN 107114-87-4 HCAPLUS

CN Guanidine, N-[3-(dimethylamino)propyl]-N'-[5-[2-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl]- (9CI) (CA INDEX NAME)



L60 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1986:61795 HCAPLUS

DOCUMENT NUMBER: 104:61795

TITLE: Pharmacological studies of pinacidil, a new antihypertensive agent. (III). General pharmacology

AUTHOR(S): Yamamoto, Kenichi; Yoshimura, Kohji; Inoue, Yuzuru; Horiuchi, Masahito; Nishimori, Tsukao; Kobayashi, Fumio; Nishimura, Keiji; Tsuchiyama, Michio

CORPORATE SOURCE: Shionogi Res. Lab., Shionogi and Co., Ltd., Osaka, 553, Japan

SOURCE: Oyo Yakuri (1985), 30(5), 897-920
CODEN: OYYAA2; ISSN: 0369-8033

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB The general pharmacol. effects of pinacidil **[60560-33-0]** and its major metabolite pinacidil-N-oxide (M-1) **[83285-82-9]** were studied by comparing these effects with those of hydralazine [86-54-4] and nifedipine [21829-25-4]. Oral administration of 2.5 mg/kg or more of pinacidil produced the following effects dose-dependently: flush on the limbs, ears, eyes, and nose, and slowness in action, hypoactivity, and ptosis in mice and rats, and hypothermia in rabbits. Pinacidil potentiated thiopental-Na-induced narcosis and tetrabenazine-induced ptosis, inhibited acetic acid-induced writhing, and increased picrotoxin-

and bicuculline-induced **convulsions** in mice. These effects were almost as potent as those of hydralazine, but more potent than those of nifedipine. Pinacidil did not affect somatic function in the traction test, rota rod performance, or righting reflex in mice, nor the conditioned responses in rats. Like hydralazine, pinacidil at a dose of 2.5 mg/kg, which caused a fall of blood pressure, did not affect the EEG pattern in conscious dogs; however, it increased the amt. of wakefulness and decreased that of slow wave sleep and fast wave sleep in the sleep-wakefulness cycles for 6 h. Pinacidil had nifedipine-like inhibitory effects on smooth muscle organs such as rabbit and guinea pig ileum and/or rat uterus, but was much weaker. It decreased urine vol. and urinary excretion of electrolytes in rats at 2.5 mg/kg or less, but decreased them at 7.5 mg/kg or more. At 2.5 mg/kg or more, it inhibited the PSP excretion. This inhibitory effect on the renal function was slightly greater than those of the ref. drugs. Pinacidil did not cause local irritation of the cornea, iris, conjunctiva, or the surface or inside of muscles in rabbits. The general pharmacol. activity of M-1 was far lower than that of the parent compd. pinacidil. The general pharmacol. activity of pinacidil is almost as high as those of hydralazine and nifedipine and the antihypertensive potency of pinacidil appears to be higher than that of hydralazine; therefore, pinacidil is considered to be a safe and efficacious drug compared with hydralazine and nifedipine.

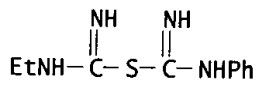
L60 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:19392 HCAPLUS
DOCUMENT NUMBER: 104:19392
TITLE: Synthesis of potential anticonvulsant and local anesthetic agents: new .alpha.,.alpha.'-thiobis(formamidine) dihydrochlorides
AUTHOR(S): Pandeya, S. N.; Yadava, M. R.; Srivastava, V.
CORPORATE SOURCE: Inst. Technol., Banaras Hindu Univ., Varanasi, 229 005, India
SOURCE: Himalayan Chemical and Pharmaceutical Bulletin (1984), 1(1), 1-3
CODEN: HCPBE5; ISSN: 0970-1281
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thioureas RCSR2 (R, R1 = H, Me, Et, CH2Ph, cyclohexyl) underwent condensation with chloroformanidines R2NHCCl:NH (R2 = H, Ph, C6H4Me-4, C6H4OMe-4) to give R2NHC(:NH)SC(:NR1)NHR (I) (13 compds.). At 50 mg/kg i.p. in rats, I (R = R1 = H, R2 = H, Ph) (II) and I (R = Et, R1 = cyclohexyl, R2 = Ph, C6H4Me-4) (III) gave 50-90% protection against electroshock-induced convulsions. II were also local anesthetics in vitro, whereas III showed little or no anesthetic activity. I (R = R1 = H, R2 = C6H4Me-4; R = Et, R1 = H, Me, R = Me, R1 = CH2Ph, R2 = C6H4Me-4), ineffective as anticonvulsants, were anesthetics in vitro. Thus, there was little correlation between anticonvulsant and anesthetic activity.

IT **1939-00-0P 2234-57-3P 3160-68-7P**
26365-08-2P 29510-13-2P 46457-07-2P
46735-10-8P 74960-95-5P 74961-38-9P
84505-95-3P 84505-96-4P 84505-97-5P
84506-06-9P 84506-07-0P 84506-08-1P
99159-61-2P 99159-62-3P 99159-63-4P
99159-64-5P 99159-65-6P 99159-66-7P
99159-67-8P 99159-68-9P 99159-69-0P
99159-70-3P 99159-71-4P 99159-72-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and anesthetic and **anticonvulsant** activity of)

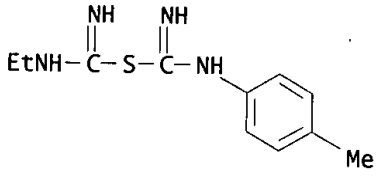
RN 1939-00-0 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N''-phenyl-, dihydrochloride (9CI)

(CA INDEX NAME)



●2 HCl

RN 2234-57-3 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N''-(4-methylphenyl)-, dihydrochloride (9CI) (CA INDEX NAME)

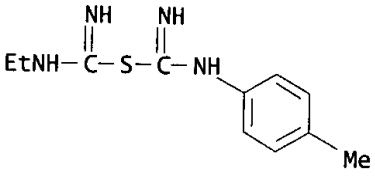


●2 HCl

RN 3160-68-7 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N'-(4-methylphenyl)-, compd. with 2,4,6-trinitrophenol (9CI) (CA INDEX NAME)

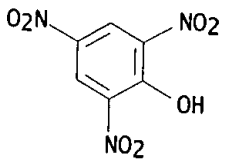
CM 1

CRN 46735-10-8
CMF C11 H16 N4 S

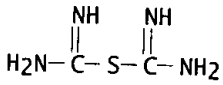


CM 2

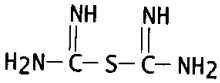
CRN 88-89-1
CMF C6 H3 N3 O7



RN 26365-08-2 HCAPLUS
CN Thiodicarbonimidic diamide (9CI) (CA INDEX NAME)

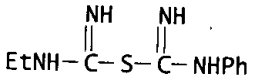


RN 29510-13-2 HCAPLUS
CN Thiodicarbonimidic diamide, dihydrochloride (9CI) (CA INDEX NAME)

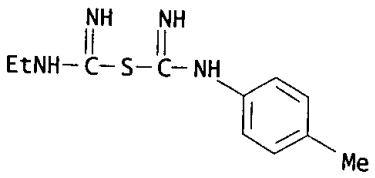


●2 HCl

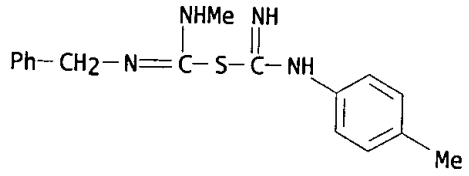
RN 46457-07-2 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N'-phenyl- (9CI) (CA INDEX NAME)



RN 46735-10-8 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N'-(4-methylphenyl)- (9CI) (CA INDEX NAME)

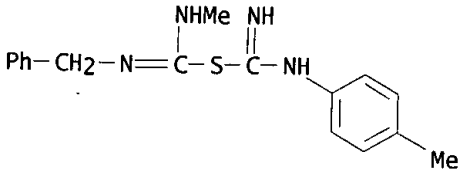


RN 74960-95-5 HCAPLUS
CN Thiodicarbonimidic diamide, N-methyl-N'-(4-methylphenyl)-N''-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

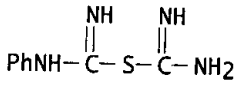


●2 HCl

RN 74961-38-9 HCAPLUS
CN Thiodicarbonimidic diamide, N-methyl-N'-(4-methylphenyl)-N''-(phenylmethyl)- (9CI) (CA INDEX NAME)

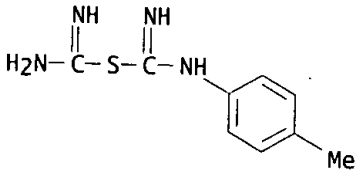


RN 84505-95-3 HCAPLUS
CN Thiodicarbonimidic diamide, phenyl-, dihydrochloride (9CI) (CA INDEX NAME)



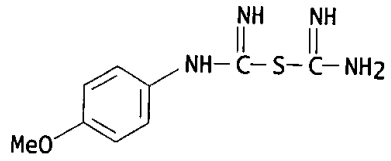
●2 HCl

RN 84505-96-4 HCAPLUS
CN Thiodicarbonimidic diamide, (4-methylphenyl)-, dihydrochloride (9CI) (CA INDEX NAME)



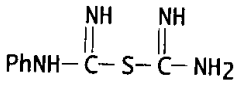
●2 HCl

RN 84505-97-5 HCAPLUS
CN Thiodicarbonimidic diamide, (4-methoxyphenyl)-, dihydrochloride (9CI) (CA INDEX NAME)

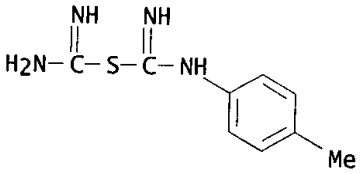


●2 HCl

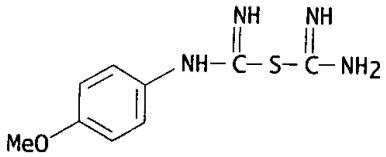
RN 84506-06-9 HCAPLUS
CN Thiodicarbonimidic diamide, phenyl- (9CI) (CA INDEX NAME)



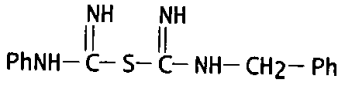
RN 84506-07-0 HCAPLUS
CN Thiodicarbonimidic diamide, (4-methylphenyl)- (9CI) (CA INDEX NAME)



RN 84506-08-1 HCAPLUS
CN Thiodicarbonimidic diamide, (4-methoxyphenyl)- (9CI) (CA INDEX NAME)

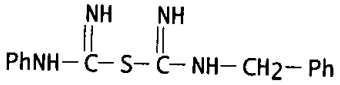


RN 99159-61-2 HCAPLUS
CN Thiodicarbonimidic diamide, N-phenyl-N'-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

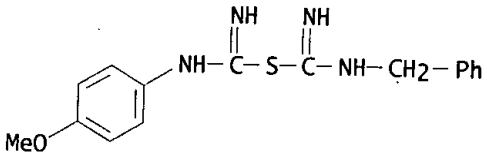


2 HCl

RN 99159-62-3 HCAPLUS
CN Thiodicarbonimidic diamide, N-phenyl-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

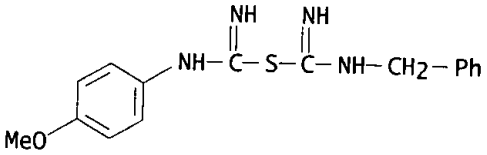


RN 99159-63-4 HCAPLUS
CN Thiodicarbonimidic diamide, N-(4-methoxyphenyl)-N'-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

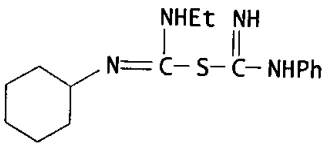


●2 HCl

RN 99159-64-5 HCAPLUS
CN Thiodicarbonimidic diamide, N-(4-methoxyphenyl)-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)

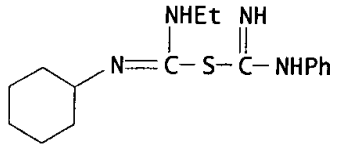


RN 99159-65-6 HCAPLUS
CN Thiodicarbonimidic diamide, N-cyclohexyl-N''-ethyl-N'-phenyl-, dihydrochloride (9CI) (CA INDEX NAME)

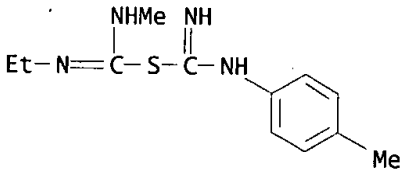


●2 HCl

RN 99159-66-7 HCAPLUS
CN Thiodicarbonimidic diamide, N-cyclohexyl-N''-ethyl-N'-phenyl- (9CI) (CA INDEX NAME)

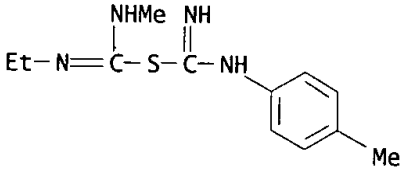


RN 99159-67-8 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N''-methyl-N'-(4-methylphenyl)-, dihydrochloride (9CI) (CA INDEX NAME)

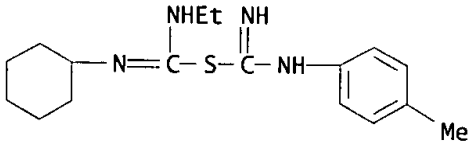


●2 HCl

RN 99159-68-9 HCAPLUS
CN Thiodicarbonimidic diamide, N-ethyl-N''-methyl-N'-(4-methylphenyl)- (9CI) (CA INDEX NAME)

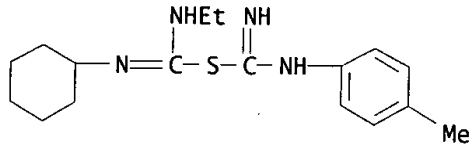


RN 99159-69-0 HCAPLUS
CN Thiodicarbonimidic diamide, N-cyclohexyl-N''-ethyl-N'-(4-methylphenyl)-, dihydrochloride (9CI) (CA INDEX NAME)

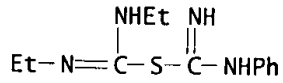


●2 HCl

RN 99159-70-3 HCAPLUS
CN Thiodicarbonimidic diamide, N-cyclohexyl-N''-ethyl-N'-(4-methylphenyl)- (9CI) (CA INDEX NAME)

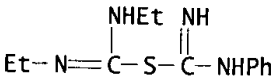


RN 99159-71-4 HCAPLUS
CN Thiodicarbonimidic diamide, N,N''-diethyl-N'-phenyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

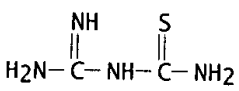
RN 99159-72-5 HCAPLUS
CN Thiodicarbonimidic diamide, N,N''-diethyl-N'-phenyl- (9CI) (CA INDEX NAME)



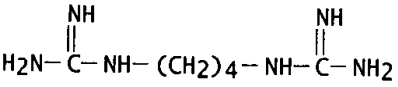
L60 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:89709 HCAPLUS
DOCUMENT NUMBER: 102:89709
TITLE: Therapeutic efficacy of berenil and imiezol against experimental Babesia canis infection in dogs
AUTHOR(S): Awaz, K. B.; Singh, Bhoop; Salabat-Ali, M.
CORPORATE SOURCE: Dep. Vet. Med., Marathwada Agric. Univ., Parbhani, 431 402, India
SOURCE: Indian Journal of Parasitology (1984), 8(1), 111-12
CODEN: IJPAES; ISSN: 0253-7168
DOCUMENT TYPE: Journal
LANGUAGE: English
AB B. canis Infection in splenectomized dogs was controlled with berenil [**908-54-3**] (10 mg/kg i.m.) and with imiezol [55750-06-6] (6 mg/kg). Berenil was free from side effects; imiezol caused dyspnea and salivation in some dogs and fatal **convulsions** in one case.

L60 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:590674 HCAPLUS
DOCUMENT NUMBER: 99:190674
TITLE: Combined effects of magnetic field and antihypoxic agents on **epileptogenic** foci in the rabbit hippocampus
AUTHOR(S): Tyvin, L. I.; Gusel, V. A.
CORPORATE SOURCE: Pediatr. Med. Inst., Leningrad, USSR
SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1983), 95(9), 29-31
CODEN: BEBMAE; ISSN: 0365-9615

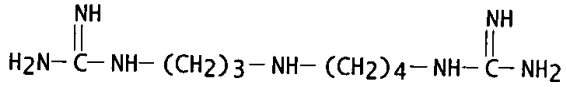
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB In rabbits, the activity of penicillin-induced **epileptogenic** foci in the hippocampus was increased by prior exposure to a magnetic field or by pretreatment with gutimine. Pretreatment with hydroxybutyrate had no effect on the hypersynchronous activity of the hippocampus. Combined magnetic field and gutimine decreased the quantity of electrog. correlates of **seizures** compared with either component alone, but the combined treatment did not affect the no. of interictal **epileptiform** discharges. Hydroxybutyrate prevented the effects of magnetic field on **epileptogenic** foci. Apparently, magnetic field induces a slight hypoxia in the hippocampus which increases **epileptogenic** foci, and this effect was inhibited by hydroxybutyrate, but not be gutimine.
IT **2114-02-5**
RL: BIOL (Biological study)
(brain hippocampus **epileptogenic** foci response to magnetic field and)
RN 2114-02-5 HCAPLUS
CN Thiourea, (aminoiminomethyl)- (9CI) (CA INDEX NAME)



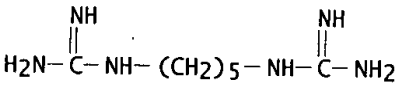
L60 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:62937 HCAPLUS
DOCUMENT NUMBER: 96:62937
TITLE: Consulsant action of diguanidine derivatives: hirudonine, arcaine and audouine
AUTHOR(S): Mori, A.; Hiramatsu, M.; Numoto, A.; Robin, Y.
CORPORATE SOURCE: Med. Sch., Okayama Univ., Okayama, 700, Japan
SOURCE: Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales (1981), 175(6), 755-60
CODEN: CRSBAW; ISSN: 0037-9026
DOCUMENT TYPE: Journal
LANGUAGE: French
AB hirudonine [2465-97-6] (0.17M) and audouine [5070-04-2] (0.22M) induced high-voltage multiple spike discharges (bursts) when applied to the sensory motor cortex area in rabbits. arcaine [544-05-8] (0.1M) induced high-voltage spike, but not bursting activity.
IT **544-05-8 2465-97-6 5070-04-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**convulsant** activity of)
RN 544-05-8 HCAPLUS
CN Guanidine, N,N'''-1,4-butanediylbis- (9CI) (CA INDEX NAME)



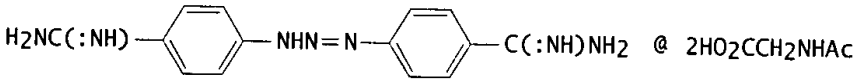
RN 2465-97-6 HCAPLUS
CN Guanidine, [3-[[4-[(aminoiminomethyl)amino]butyl]amino]propyl]- (9CI) (CA INDEX NAME)



RN 5070-04-2 HCAPLUS
CN Guanidine, N,N'''-1,5-pentanediylbis- (9CI) (CA INDEX NAME)



L60 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:597415 HCAPLUS
DOCUMENT NUMBER: 95:197415
TITLE: Toxicity of diminazene aceturate (berenil) to camels
AUTHOR(S): Homeida, A. M.; El Amin, E. A.; Adam, S. E. I.; Mahmoud, M. M.
CORPORATE SOURCE: Dep. Vet. Clin. Stud., Univ. Khartown, Khartoum North, Sudan
SOURCE: Journal of Comparative Pathology (1981), 91(3), 355-60
CODEN: JCVPAR; ISSN: 0021-9975
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Three dromedary camels administered berenil (I) [**908-54-3**] (10 or 40 mg/kg) showed acute symptoms of neurotoxicity manifested by hyperesthesia, salivation, intermittent **convulsions**, frequent urination and defecation, itching, and sweating. One animal died 4 h later, another 8 days later, and the 3rd was killed on the 8th day. Liver and kidney damage were obsd. The aspartic aminotransferase [9000-97-9] and NH3 levels of blood serum were increased, the Ca and Mg levels were decreased, and no significant changes in the concn. of total protein, alanine aminotransferase [9000-86-6], and bilirubin [635-65-4] were obsd. ATPase [9000-83-3], 5-nucleotidase [9027-73-0], succinic tetrazolium reductase [37217-40-6], and glucose 6-phosphatase [9001-39-2] of the liver and kidney cells were decreased.

L60 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:581115 HCAPLUS
DOCUMENT NUMBER: 95:181115
TITLE: Systemic effects of oral use of chlorhexidine gel in multihandicapped epileptic children
AUTHOR(S): Russell, Bjoern G.; Bay, Lena M.
CORPORATE SOURCE: Dep. Dent. Serv., Child. Hosp. Vangede, Copenhagen, Den.

SOURCE: Scandinavian Journal of Dental Research (1981), 89(3), 264-9
CODEN: SJDRAN; ISSN: 0029-845X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of the daily use of a toothpaste contg. 1% corsodyl (chlorhexidine gluconate) [**18472-51-0**] on blood compn. and liver function in multihandicapped **epileptic** children over a 2-mo period. Although certain abnormalities in hematol. and biochem. blood tests were recorded both prior to and after treatment, the prevalence of abnormalities was similar in the chlorhexidine and control groups, even though the patients in the study constituted a high risk group because of multiple drug therapy.

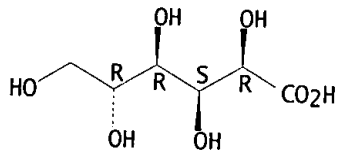
IT **18472-51-0**
RL: BIOL (Biological study)
(toothpaste contg., blood compn. and liver function in **epilepsy** response to)

RN 18472-51-0 HCAPLUS
CN D-Gluconic acid, compd. with N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide (2:1) (9CI) (CA INDEX NAME)

CM 1

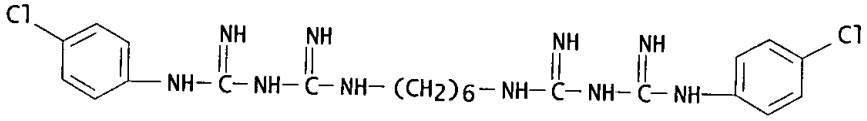
CRN 526-95-4
CMF C6 H12 O7

Absolute stereochemistry.



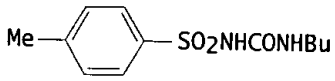
CM 2

CRN 55-56-1
CMF C22 H30 Cl2 N10



L60 ANSWER 32 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:509637 HCAPLUS
DOCUMENT NUMBER: 95:109637
TITLE: Brain GABA and cyclic GMP as indexes of metabolic lesions in CNS oxygen toxicity
AUTHOR(S): Radomski, M. W.; Watson, W. J.
CORPORATE SOURCE: Def. Civ. Inst. Environ. Med., Downnsview, ON, Can.
SOURCE: Underwater Physiology (1981), 7, 121-8
CODEN: UNPHD4; ISSN: 0082-0997
DOCUMENT TYPE: Journal

LANGUAGE: English
GI

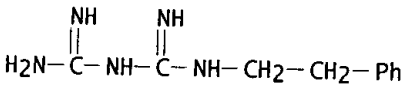


I

AB Tolbutamide (I) [64-77-7], Tris [77-86-1], NaHCO3, Na succinate [14047-56-4], glutathione [70-18-8], L-cysteine [52-90-4] and succinate or glutamate [56-86-0], and pargyline [555-57-7] protected against O **convulsions** and against O-induced decrease in GABA [56-12-2] of brain. Acetohexamide [968-81-0] was without effect and phenformin [**114-86-3**] potentiated **convulsions**. Disulfiram [97-77-8] increased the Convusion Redn. Factor without any effect on the O-induced decrease in GABA. Diazepam [439-14-5] (4 and 8 .mu.mol/kg) delayed the onset of O-induced **convulsions**, but had no effect on the GABA decrease. Although hyperbaric O (HBO) did not alter cGMP [7665-99-8] in the brain, the ratio of cGMP/GABA was increased by HBO due to an increase in GABA.

IT **114-86-3**
RL: BIOL (Biological study)
(oxygen-induced changes in brain GABA and **convulsions** response to)

RN 114-86-3 HCAPLUS
CN Imidodicarbonimidic diamide, N-(2-phenylethyl)- (9CI) (CA INDEX NAME)



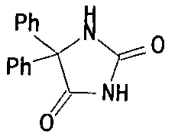
L60 ANSWER 33 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:508785 HCAPLUS
DOCUMENT NUMBER: 95:108785
TITLE: Mechanism of respiratory and cardiovascular changes by pulmonary chemoreflexes
AUTHOR(S): Tomori, Z.; Javorka, K.
CORPORATE SOURCE: Fac. Med., Comenius Univ., Martin, Czech.
SOURCE: Atemwegs- und Lungenkrankheiten (1981), 7(3), 145-7
CODEN: ATLUDF; ISSN: 0341-3055
DOCUMENT TYPE: Journal
LANGUAGE: German

AB Injection of 1,1-dimethyl-4-phenylpiperazine iodide [54-77-3], micoren [8015-51-8], phenylbiguanide [**102-02-3**], or Na salicylate [54-21-7] into cats or rabbits evoked a respiratory reaction that resembled a chemoreflex more than a cough. This reflex was composed of 2 more or less antagonistic phases: an initial fall in breathing rate and blood pressure, followed by a rise. Micoren injection frequently elicited marked expiratory and(or) inspiratory efforts, accompanied by general **convulsions**.

L60 ANSWER 34 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:114469 HCAPLUS
DOCUMENT NUMBER: 94:114469
TITLE: The effect of the combined administration of

diphenylhydantoin and certain oral hypoglycemics on the contents of some vitamins of the B-complex group

AUTHOR(S): Saad, Samir F.; Shehata, M. M.
CORPORATE SOURCE: Fac. Pharm., Cairo Univ., Cairo, Egypt
SOURCE: Journal of Drug Research (1979), 11(1-2), 93-100
CODEN: JDGRAX; ISSN: 0368-1866
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Diphenylhydantoin (I) [630-93-3] (50 and 100 mg/kg/day for 3 wk) given i.p. to rats dose-dependently decreased the liver levels of thiamin [59-43-8], riboflavin [83-88-5], niacin [59-67-6], and pantothenic acid [79-83-4]. The hepatic thiamin content was normalized by simultaneous administration of either acetohexamide [968-81-0] or phenformin [**114-86-3**] (100 and 50 mg/kg/day, resp., for 7 days), but the other vitamins were unaffected or were not fully returned to normal. Apparently, administration of vitamin B is necessary for **epileptic** patients treated with I or for diabetic **epileptics** treated with I plus oral hypoglycemics.

L60 ANSWER 35 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:462532 HCAPLUS
DOCUMENT NUMBER: 93:62532
TITLE: Effect of guanidino compounds on glutamic pyruvic transaminase, glutamic oxalacetic transaminase and glutamic acid decarboxylase in mouse brain

AUTHOR(S): Shindo, Shoichiro; Katayama, Yasuto; Mori, Akitane; et al.
CORPORATE SOURCE: Inst. Neurobiol., Okayama Univ. Med. Sch., Okayama, Japan
SOURCE: Neurosciences (Okayama, Japan) (1979), 5(1), 96-7
CODEN: NUOCDO; ISSN: 0388-7448
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Since guanidino compds. are known to induce **epilepsy**, effects of 34 guanidino compds. on brain enzymes were studied. Only 4 compds., arcaine [**544-05-8**], audouine [**5070-04-2**], creatine [57-00-1], and creatinine [60-27-5] inhibited glutamic pyruvic transaminase [9000-86-6] of mouse brain in vitro, and none of the 34 compds. inhibited glutamate oxalate transaminase [61461-53-8] or glutamate decarboxylase [9024-58-2]. Dipropylacetic acid [99-66-1], an **antiepileptic**, showed no effect on these enzymes, indicating that the **antiepileptic** activity of this drug is not mediated by these enzymes. However, aminoxyacetic acid [645-88-5], an inhibitor of .gamma.-aminobutyrate transaminase, markedly inhibited the title enzymes.

L60 ANSWER 36 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1979:391 HCAPLUS
DOCUMENT NUMBER: 90:391
TITLE: Effects of lidamidine hydrochloride (WHR-1142A), a

novel antidiarrheal agent on the cardiovascular and central nervous systems

AUTHOR(S): Riley, R. L.; Mir, G. N.; Rowles, G. S.; Sperow, J. W.; Alioto, R. L.; Yelnosky, J.

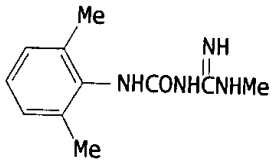
CORPORATE SOURCE: William H. Rorer, Inc., Fort Washington, PA, USA

SOURCE: Arzneimittel-Forschung (1978), 28(8A), 1461-6
CODEN: ARZNAD; ISSN: 0004-4172

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB Lidamidine-HCl (I-HCl) [**65009-35-0**] at 1 mg/kg i.v., reduced cardiac output in the anesthetized dog primarily by depressing heart rate; the blood pressure was slightly elevated due to an increase in peripheral resistance. I was effective in reverting ouabain-induced ventricular arrhythmias to a sinus rhythm. Unlike diphenoxylate, I did not potentiate the central nervous system (CNS) depressant effects of hexobarbital or ethanol. I did not block pentetrazole-induced **convulsions**, electroshock **seizures** or amphetamine aggregate toxicity. At high doses I caused a general CNS depressant effect which was not related to a neuroleptic- or barbiturate-like action.

L60 ANSWER 37 OF 38 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1975:527078 HCAPLUS

DOCUMENT NUMBER: 83:127078

TITLE: Effect of natural antioxidants and radioprotectants on acute oxygen toxicity and brain .gamma.-aminobutyric acid in rats

AUTHOR(S): Radomski, M. W.; Watson, W. J.; McBurney, L. J.

CORPORATE SOURCE: Def. Civ. Inst. Environ. Med., Downsview, ON, Can.

SOURCE: Int. Hyperbaric Congr. Proc., 5th (1974), Meeting Date 1973, Volume 1, 142-9. Editor(s): Trapp, W. G.; Banister, E. W.; Davison, A. J. Simon Fraser Univ.: Burnaby, Can.
CODEN: 30XAAO

DOCUMENT TYPE: Conference

LANGUAGE: English

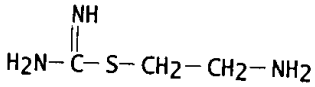
AB The radioprotective agents S-(2-aminoethyl)isothiourea [**151-16-6**], .beta.-mercaptoethylamine [60-23-1], glutathione [70-18-8] and particularly 2-methyl-2-thiopseudourea sulfate [2260-00-6] administered i.p. prevented the **convulsions** induced in rats by exposure to high pressure oxygen [7782-44-7]. All 4 agents blocked the decrease in brain GABA [56-12-2] which precedes **convulsions**. The antioxidant selenomethionine [1464-42-2] or vitamin E [1406-18-4] itself had no effect on the **convulsions**. The carriers of vitamin E, Tween 80 [9005-65-6] and propylene glycol [57-55-6], sightly prevented the **convulsions** and prevented decrease in brain GABA level.

IT **151-16-6**

RL: BIOL (Biological study)

(**convulsions** from oxygen prevention by, brain GABA in

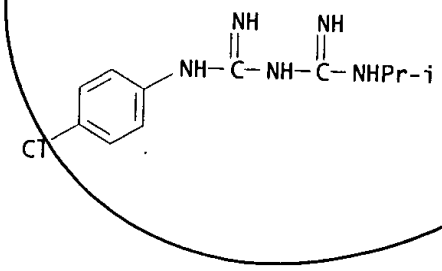
relation to)
RN 151-16-6 HCAPLUS
CN Carbamimidothioic acid, 2-aminoethyl ester (9CI) (CA INDEX NAME)



L60 ANSWER 38 OF 38 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1964:41492 HCAPLUS
DOCUMENT NUMBER: 60:41492
ORIGINAL REFERENCE NO.: 60:7332c-e
TITLE: Anticonvulsant and antifibrillatory drugs
AUTHOR(S): Bose, B. C.; Saifi, A. Q.; Sharma, S. K.
CORPORATE SOURCE: M. G. M. Med. Coll., Indore, India
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1963), 146(1/2), 106-13
CODEN: AIPTAK; ISSN: 0003-9780
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB The proposed basic mechanisms (interpreted) for cardiac dysrhythmia differ considerably. Since there is some evidence that acetyl-choline (I) may be involved, new expts. were done to det. the effects of various drugs on I synthesis. Adult albino rats of both sexes (100-150 g. wt.) were used. I of the brain and heart was detd. (by frog rectus abdominis muscle assay) before and after short and long-term (3 weeks) drug treatment. Quant. data for I are tabulated in relation to the drugs used. Both short and long-term dosage with chlorpromazine (II) promethazine, (III), or quinidine (IV) reduced I in the brain. Brief treatment with II, III, IV, Paludrine (V), Thiantoin (VI), Mysoline (VII), Dilantin (VIII), Tridione, or Milontin diminished I in the heart. II, III, IV, or Paludrine provided some protection against minimal electroshock seizures in rats. II, III, VI, VII, VIII, or Mesantoin showed various degrees of antifibrillatory activity against auricular fibrillation induced by exogenous I in dogs. The results indicated that changes in I levels were part of the mechanisms by which various compds. exerted an anticonvulsant or antifibrillatory effect, but did not exclude the possibility that other chem. and phys. mechanisms were also involved. 15 references.

IT **500-92-5**, Biguanide, 1-(p-chlorophenyl)-5-isopropyl-
(effect on acetylcholine formation by brain and heart, **anticonvulsant** and antifi-brillatory drugs in relation to)
RN 500-92-5 HCAPLUS
CN Imidodicarbonimidic diamide, N-(4-chlorophenyl)-N'-(1-methylethyl)- (9CI) (CA INDEX NAME)



Inventor Search

KIM 09/881,215

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     FILE 'HCAPLUS' ENTERED AT 11:34:22 ON 17 JUL 2003
L1          284 S CROOKS P?/AU
L2          102 S BENCE A?/AU
L3           26 S WORTHEN D?/AU
L4          390 S L1-3
L5            2 S L4 AND AGMATINE
                SELECT RN L5 1-2

     FILE 'REGISTRY' ENTERED AT 11:35:09 ON 17 JUL 2003
L6            1 S E1

     FILE 'HCAPLUS' ENTERED AT 11:35:19 ON 17 JUL 2003
L7            2 S L5 AND L6
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2 cites

1 compound disclosed in the L5 cites

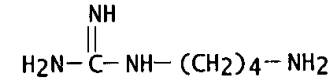
2 cites w/ 1 cpd. disclosed

=> d ibib abs hitstr ind 1-2

L7 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:49216 HCAPLUS
TITLE: An in vivo evaluation of the antiseizure activity and acute neurotoxicity of **agmatine**
AUTHOR(S): **Bence, Aimee K.**; **Worthen, David R.**; Stables, James P.; **Crooks, Peter A.**
CORPORATE SOURCE: College of Pharmacy, Division of Pharmaceutical Sciences, University of Kentucky, Lexington, KY, 40536-0082, USA
SOURCE: Pharmacology, Biochemistry and Behavior (2003), 74(3), 771-775
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Agmatine**, an endogenous cationic amine, exerts a wide range of biol. effects, including modulation of glutamate-activated N-methyl-d-aspartate (NMDA) receptor function in the central nervous system (CNS). Since glutamate and the NMDA receptor have been implicated in the initiation and spread of seizure activity, the capacity of **agmatine** to inhibit seizure spread was evaluated in vivo. Orally administered **agmatine** (30 mg/kg) protected against maximal electroshock seizure (MES)-induced seizure spread in rats as rapidly as 15 min and for as long as 6 h after administration. Inhibition of MES-induced seizure spread was also obsd. when **agmatine** was administered i.p. **Agmatine**'s antiseizure activity did not appear to be dose-dependent. An in vivo neurotoxicity screen indicated that **agmatine** was devoid of any acute neurol. toxicity at the doses tested. These preliminary data suggest that **agmatine** has promising anticonvulsant activity.

IT **306-60-5, Agmatine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiseizure activity and acute neurotoxicity of **agmatine**)
RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



CC 1-11 (Pharmacology)
ST anticonvulsant **agmatine** neurotoxicity seizure
IT Anticonvulsants
Seizures
(antiseizure activity and acute neurotoxicity of **agmatine**)
IT Toxicity
(neurotoxicity; antiseizure activity and acute neurotoxicity of **agmatine**)
IT Nerve
(toxicity; antiseizure activity and acute neurotoxicity of **agmatine**)
IT **306-60-5, Agmatine**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antiseizure activity and acute neurotoxicity of **agmatine**)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

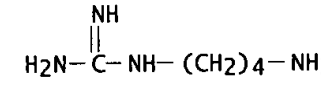
L7 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:923603 HCAPLUS
DOCUMENT NUMBER: 136:31716
TITLE: **Agmatine** and **agmatine** analogs in the treatment of epilepsy, seizure, and electroconvulsive disorders
INVENTOR(S): **Crooks, Peter A.; Bence, Aimee K.; Worthen, David R.**
PATENT ASSIGNEE(S): University of Kentucky Research Foundation, USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001095897	A1	20011220	WO 2001-US19095	20010615
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002065323	A1	20020530	US 2001-881215	20010615

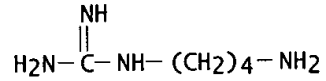
PRIORITY APPLN. INFO.: US 2000-211532P P 20000615
OTHER SOURCE(S): MARPAT 136:31716

AB Pharmaceutical prepns. contg. of **agmatine**, congeners, analogs or derivs. thereof for use in preventing or treating epilepsy, seizures, and other electroconvulsive disorders, are provided. Embodiments include administering an effective amt. of **agmatine**, an **agmatine** analog or a pharmaceutically acceptable salt thereof to a human subject in need of treatment or prevention of epilepsy, seizure or other electroconvulsive disorder to treat, reduce, or prevent the disorder in the subject.

IT **306-60-5, Agmatine 306-60-5D, Agmatine**, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



RN 306-60-5 HCAPLUS
CN Guanidine, (4-aminobutyl)- (8CI, 9CI) (CA INDEX NAME)



IC ICM A61K031-155
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
ST **agmatine** epilepsy seizure electroconvulsive disorder
IT Brain
(EEG; **agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
IT Anticonvulsants
Drug delivery systems
Nervous system agents
Seizures
(**agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
IT Nervous system, disease
(electroconvulsive disorder; **agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
IT Drug delivery systems
(oral; **agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
IT Drug delivery systems
(parenterals; **agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
IT **306-60-5, Agmatine 306-60-5D, Agmatine**
, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**agmatine** and **agmatine** analogs for treatment of epilepsy, seizure, and electroconvulsive disorders)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2: Entry 3 of 11 File: USPT Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6291247 B1
TITLE: Methods of screening for factors that disrupt neurotrophin conformation and reduce neurotrophin biological activity

Brief Summary Text (10):
NGF, a 118 amino acid protein, is an extremely important neurotrophin, being implicated in the pathogenesis of Alzheimer's disease, epilepsy and pain. The binding of NGF to its receptors is determined by distinct sequences within its primary amino acid structure The hairpin loop at residues 29-35 is responsible for recognition by p75.sup.NTR, while the amino and carboxy termini are important binding determinants for recognition by the TrkA receptor NGF exerts its biological activity as a non-covalent dimer. Two 118 residue NGF monomers are dimerized by hydrophobic and van der Waals interacts between their three anti-parallel pairs of .beta.-strands. Consequently, the amino terminus of a first NGF protomer and the carboxyl terminus of a second NGF protomer are spatially juxtaposed, and the amino terminus of the second NGF protomer and the carboxyl terminus of the first NGF protomer are spatially juxtaposed. Furthermore, although the NGF dimer thus has 2 pairs of termini, only one pair of termini is required for TrkA receptor recognition.

Brief Summary Text (15):
The neurotrophins function primarily to promote survival of certain classes of peripheral and central neurons both during development and following neuronal damage. NGF, in particular, is involved with the development of neurons in the peripheral nervous system and supports neuronal survival, as well as enhancing and maintaining the differentiated state of neurons. Several lines of evidence also suggest that NGF may mediate inflammation (Levi-Montalcini, Science 237: 1154-1162 (1987)). However, in some neurological disease states, the neurotrophins may also support inappropriate neurite outgrowth thereby facilitating the progression of a disease condition. For example, neurotrophins promote the undesirable sprouting of hippocampal "mossy fibres". Such inappropriate sprouting of mossy fibers is a common accompaniment of epilepsy in humans. In other pathological states, such as Alzheimer's disease, as mentioned above, aberrant process growth, known as dystrophic neurite formation, is a strong correlate of disease severity.

Drawing Description Text (6):
FIG. 4 illustrates the effects of the peptides of FIG. 3 on kindling-induced seizures.

Detailed Description Text (18):
Peptide R11 effectively inhibited the neurite growth of embryonic day 8 (ED8) chick dorsal root ganglion (DRG) neurons in vitro (Sutter et al., J. Biol. Chem. 254: 5972-5982 (1979)) with an IC.sub.50 of 10 .mu.M, as shown in FIG. 6. The dose response profile for the peptide displayed a shallow inhibition curve over a wide concentration range. Such a profile is not typical of a competitive inhibitor. That is, a different dose response profile would be expected if R11 were simply competing with NGF for binding to a receptor. Neither of the less constrained synthetic Intermediates of R11, i.e., R11 (linear) or R11 (monocyclic), was as effective in blocking NGF-dependent neurite growth concentrations up to 200 .mu.M. This indicates that the R11 peptide with its two disulfide bridges has differences in its conformation that lead to differences in its unction. R11 was also shown to inhibit both seizure and mossy fiber sprouting in an animal model of epilepsy whereby repeated subconvulsive electrical stimulation of the forebrain leads to a progressive and permanent amplification of seizure activity (kindling) (Rashid et al., Proc. Natl. Acad. Sci. USA 92: 9495-9499 (199). Indeed we have demonstrated that R11 is an effective antagonist of BDNF and NT-3 in vitro (Rashid et al., Proc.

Natl. Acad. Sci. USA 92: 9495-9499 (1995)).

Detailed Description Text (32):
In the case of depsi-bicyclic peptides it will be appreciated that the N- and C-termini remain as free amino and free carboxyl residues, respectively, since it is the side chains of the terminal amino acids which are involved in the covalent cyclizing linkage The free terminal amino and carboxyl groups may also be derivative or altered without affecting the activity of the peptide as an inhibitor of a neurotrophin-mediated activity. For example, the termini may be derivative to include a non-peptidic blocking group Fat will prevent potential degradation at the N- and C-terminal ends from occurring. Such non-peptidic groups include protecting groups such as those conventionally used in the art of peptide synthesis which will not adversely affect the in vitro and in vivo uses of the bicyclic peptide. For example, suitable non-peptidic N-terminal blocking groups can be introduced by alkylation or acylation of the N-terminus. Examples of suitable N-terminal blocking groups include C.sub.1 -C.sub.5 branched or unbranched alkyl groups, acyl groups such as formyl and acetyl groups, as well as substituted forms thereof. Amino acid analogues lacking the amino functionality are also useful to block the N-terminus. Suitable non-peptidic C-terminal blocking groups, in which the carboxyl group of the C-terminus may be either incorporated or not, include esters, ketones or amides. Ester or ketone-forming alkyl groups, particularly lower alkyl groups such as methyl, ethyl and propyl, and amide-forming amino groups such as primary amines (--NH.sub.2), and mono and di-alkylamino groups such as methylamino, ethylamino, dimethylamino, diethylamino, methylbutylamino and the like are examples of C-terminal blocking groups. Amino acid analogues lacking the carboxyl functionality are also useful C-terminal blocking groups such as agmatine. Further, it will be appreciated that the free amino and carboxyl groups at the termini can be removed altogether from the bicyclic peptide to yield desamino and descarboxylated forms thereof without e on peptide activity.

Detailed Description Text (50):
Compositions for in vivo administration, e.g., for treating neurological conditions such as epilepsy or Alzheimer's disease, are also contemplated. Such compositions comprise a therapeutically effective amount of a bicyclic peptide together with a pharmaceutically acceptable carrier. In this context, the term "pharmaceutically acceptable" means acceptable for use in the pharmaceutical and veterinary arts, i.e., non-toxic and not adversely affecting the activity of the bicyclic peptide. The term "therapeutically effective amount" means an amount of the compound sufficient to reduce undesirable neurotrophin-mediated activity, as determined using assays of conventional design such as the assays described herein in the specific examples, in an afflicted individual without causing adverse effects.

Detailed Description Text (83):
Kindling is a phenomenon in which repeated low-intensity (subconvulsive) electrical stimulation of forebrain areas leads to a progressive and permanent amplification of seizure activity, and is, thus, widely accepted as a model for human temporal lobe epilepsy. The effect of the present neurotrophin-derived peptides on kindling was determined as follows.

Detailed Description Text (85):
Following a three-day recovery, the kindling stimulations were started. The animals received a one-second train of one-millisecond pulses at a frequency of 60 Hz and a pulse intensity of 200-400 .mu.A. These pulses were sufficient to trigger an epileptiform afterdischarge (AD) following each stimulation. Each animal was stimulated in this fashion twice a day over a period of 11 days. Progression of kindling was monitored behaviorally and electrophysiologically by recording the behavioral seizure stages and the duration and magnitude of afterdischarges. Fully kindled animals exhibited three consecutive stage-5 seizures (Racine, Electroencephalogr. Clin. Neurophysiol., 32:281 (1972)).

Detailed Description Text (86):
The number of stimulations to reach stage-5 seizures for control rats and rats receiving the linear, cyclic and bicyclic peptides is illustrated graphically in FIG. 4. The results illustrate that the bicyclic peptide has a potency which is approximately equal to that of the anti-NGF IgG in delaying the onset of kindling in

comparison to the control serum IgG, linear peptide and cyclic peptide.

Detailed Description Text (94):
Although Zn.sup.2+ and neurotrophins have been implicated in the pathogenesis of neurological disease states, such as stroke (Koh, J.-Y. et al. The role of zinc in selective neuronal death after global cerebral ischemia. Science 272, 1013-1016 (1996))., Alzheimer's disease (Rylett, R. J. & Williams, L. R. Role of neurotrophins in cholinergic-neurone function in the adult and aged CNS. Trends Neurosci. 17, 490 (1994)), epilepsy (Ben-Ari, Y. & Represa, A. Brief seizure episodes induce long-term potentiation and mossy fiber sprouting in the hippocampus. Trends Neurosci. 13, 312-318 (1990); Rashid, K. et al. A nerve growth factor peptide retards seizure development and inhibits neuronal sprouting in a rat model of epilepsy. Proc. Natl. Acad. Sci. USA 92, 9495-9499 (1995)), Zn.sup.2+ inactivation of neurotrophins may mitigate neural cell death via a p75.sup.NTR mediated signal (Frade, J. M., Rodriguez-Tebar, A. & Barde, Y.-A. Induction of cell death by endogenous nerve growth factor through its p75 receptor. Nature 383, 166-168 (1996), Casaccia-Bonnefil, P., Carter, B. D., Dobrowsky, R. T. & Chao, M. V. Death of oligodendrocytes mediated by the interation of nerve growth factor with its receptor p75. Nature 383, 716-719 (1996), and Van der Zee, C. E. E. M., Ross, G. M., Riopelle, R. J. & Hagg, T. Survival of cholinergic forebrain neurons in developing p75.sup.NGFR deficient mice. Science 274, 1729-1732 (1996)) under specfic conditions. Further, in cases where activity appears to have detrimental effects (pain, inflammation (Lewin, G. R. & Mendell, L. M. Nerve growth factor and nociception. Trends Neurosci. 16, 353-359 (1993); Woolf, C. J. & Doubell, T. A. The pathophysiology of chronic pain--increased sensitivity to low threshold A.beta.-fiber inputs. Curr. Opin. Neurbiol. 4, 525-534 (1994); McMahon, S. B., Bennett, D. L. H., Priestley, J. V. & Shelton, D. L. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-lgG fusion molecule. Nature Med. 1, 774-780 (1994)), cell deaths, inhibition of neurotrophin activity using similar approaches are contemplated to have therapeutic utility.

Detailed Description Text (96):
Zn.sup.2+ is a critical component of many proteins and plays a key role in a host of biological processes. In particular, Zn.sup.2+ serves both catalytic and structural roles in many proteins. Within the central nervous system, certain regions contain relatively high concentrations of Zn.sup.2+ packaged in presynaptic vesicles (Smart T. G., Xie, X & Krishek, B. J. Modulation of inhibitory and excitatory amino acid receptor ion channels by zinc. Prog. Neurobiol. 42, 393-441 (1994)). The release and translocation of Zn.sup.2+ upon chemical or electrical stimulation has been demonstrated, and concentrations of 100-300 .mu.M at synapses have been reported (Xie, X. & Smart, T. G. A physiological role for endogenous zinc in rat hippocampal synaptic neurotransmission. Nature 349, 521-524 (1991)). The ability of Zn.sup.2+ to interact with a variety of target proteins and peptides has led to the development of several models of disease states where neuronal dysfunction or degeneration may be induced by a Zn.sup.2+ regulation. Such systems include the interactions of Zn.sup.2+ with amyloid .beta. protein in the pathogenesis of Alzheimer's disease (Bush, A. I. et al. Rapid induction of Alzheimer A.beta. amyloid formation by zinc. Science 265, 1461-1487 (1993), modulation of ligand- and voltage-gated ion channels as implicated in epilepsy (Harrison, N. L. & Gibbons, S. J. Zn.sup.2+ : An endogenous modulator of ligand- and voltage-gated ion channels. Neurophrmacol. 33, 935-952 (1994)), and a possible role in the neuronal death observed after cerebral ischemia (Koh, J.-Y. et al. The role of zinc in selective neuronal death after global cerebral ischemia. Science 272, 1013-1016(1996)).

Detailed Description Text (133):
To the extent that Zn.sup.2+ and neurotrophins have been implicated in the pathogenesis of neurological disease states (e.g. stroke, Alzheimer's disease, epilepsy), the present studies provide one mechanism to suggest that a Zn.sup.2+ -neurotrophin in interaction may be deleterious. Alternatively, under specific conditions, Zn.sup.2+ inactivation of neurotrophins may mitigate neural cell death via a p75.sup.NTR mediated signal. The recognition that aberrant Zn.sup.2+ regulation may induce neuronal damage by a specific interaction with a neurotrophin will provide additional strategies for therapeutic intervention. Further, in cases where activity appears to have detrimental effects (pain, inflammation (Lewin, G. R.

& Mendell, L. M. Nerve growth factor and nociception. Trends Neurosci. 16, 353-359 (1993), Woolf, C. J. & Doubell, T. A. The patophysiology of chronic pain--increased sensitivity to low threshold A.beta.-fiber inputs. Curr. Opin. Neurobiol. 4, 525-534 (1994), and McMahon, S. B., Bennett, D. L. H., Priestley, J. V. & Shelton, D. L. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-IgG fusion molecule. Nature Med. 1, 774-780 (1994)), cell death (Frade, J. M., Rodriguez-Tebar, A. & Barde, Y.-A. Induction of cell death by endogenous nerve growth factor through its p75 receptor. Nature 383, 166-168 (1996), Casaccia-Bonnefil, P., Carter, B. D., Dobrowsky, R. T. & Chao, M. V. Death of oligodendrocytes mediated by the interaction of nerve growth factor with its receptor p75. Nature 383, 716-719 (1996)). Inhibition of neurotrophin activity using similar approaches are contemplated to have therapeutic utility.

Other Reference Publication (10):
Ben-Ari, et al., "Brief seizure episodes induce long-term potentiation and mossy fibre sprouting in the hippocampus", TINS 13(8): 312-318 (1990).

Other Reference Publication (19):
Rashid, et al., "A nerve growth factor peptide retards seizure development and inhibits neuronal sprouting in a rat model epilepsy", Proc. Natl. Acad. Sci. USA 92: 9495-9499 (1995).

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L2: Entry 6 of 11 File: USPT Jul 11, 1995

DOCUMENT-IDENTIFIER: US 5432202 A
TITLE: Use of polyamines as ionic-channel regulating agents

Brief Summary Text (20):
The calcium channel modulators of the present invention also have potential uses as prototypic drugs exhibiting anticonvulsant (e.g. anti-epileptic), anxiolytic, tranquilizing, anti-Alzheimer's, and/or memory-improving properties.

Detailed Description Text (25):
For example, decarboxylated arginine (agmatine), or arginine ethyl ester, decarboxylated lysine or lysine methyl or ethyl ester can be purchased from Sigma Chemical Co., St. Louis, Mo. Other well known polyamines such as spermine, spermidine, 1,6 diaminohexane and other diaminoalkanes, can also be obtained from Sigma or other commercial sources. Those polyamines which are not themselves active (e.g., spermine) can be used to synthesize active compounds as follows:

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A LCOHOLISM : C LINICAL AND E XPERIMENTAL R ESEARCH

Role of Polyamines and NMDA Receptors in Eth Dependence and Withdrawal

John M. Littleton, David Lovinger, Sture Liljequist, Raj Ticku, Izuru Matsumoto, and Susan Barron

This article represents the proceedings of a symposium at the 2000 ISBRA Meeting in Yokohama, Japan. The chair was John M. Littleton. The presentations were (1) Examination of ethanol spermine and acamprosate actions on native and recombinant NMDA receptors, by David Lovinger; (2) Ethanol inhibition of NMDA neurotoxicity on the polyamine site in cerebellar granule cells, by Sture Liljequist; (3) Alterations in expression of NMDA receptor subunits during ethanol exposure and withdrawal, by Raj Ticku; (4) Alterations in polyamine synthesis and release as a potential mechanism for ethanol dependence and withdrawal, by Izuru Matsumoto; (5) The role of polyamines in neurotoxicity induced by alcohol withdrawal in vitro, by John Littleton; and (6) Agmatine reduces some of the effects of "third trimester" alcohol exposure using a rodent model, by Susan Barron.

Key Words: Seizures, Neurotoxicity, NMDA, Subunits, Ifenprodil, Acamprosate.

POLYAMINES ARE SIMPLE, ubiquitous compounds found in plants and animals. The major pathway for their synthesis in mammals is from ornithine to putrescine and then to the most important polyamines—spermine and spermidine. The rate-limiting step in this pathway is regulated by ornithine decarboxylase. Their small size, flexibility, and multiple amine groups enable these polyamines to bind to several sites in mammalian tissues. The affinity of the polyamines for many types of receptors and ion channels (Williams, 1997) at which ethanol is also believed to act suggests many potential interactions between the agents. The focus of this review is the ability of polyamines and ethanol to interact with the glutamate/NMDA receptor (NMDAR). One of the major known physiological functions of polyamines is in cell growth and division; thus, the NMDARs expressed in developing brain a sensitive to the potentiating effects of these po (Sircar, 2000). Because NMDAR activity is as important neurotrophic effects on neuronal gr tion, and synapse formation in the developing been suggested that positive modulation of NM polyamines may contribute to these effects (Jo 1996). Interactions with these "beneficial" eff amines therefore could be of particular import effects of alcohol on CNS development, for ex fetal alcohol syndrome. Later in life, polyamin darker side and are implicated in unrestricted and division, as in some cancers. They continu tiate NMDAR function in the adult CNS, and pathophysiological relevance, which probably

inhibition of polyamine synthesis in the neonatal rat markedly reduces viable neurons in the adult animal, particularly in the cerebellum (Sparapini et al., 1996). One mechanism for this effect may be the ability of polyamines to potentiate the function of NMDARs. Polyamine levels in the central nervous system (CNS) are highest during development, and

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to hyperexcitability states such as seizures (Do Shaw, 1996; Laschet et al., 1992) and to excit neurotoxicity (Fahey et al., 1993). Once again, between ethanol and polyamines are clearly of importance in relationship to many of the sequ ethanol abuse, which include ethanol withdrav This brief review will concentrate on NMDAR and how this is altered by polyamines during c sure to, and withdrawal from, ethanol. A majo the potential for therapeutic intervention at the site(s) on NMDARs.

The NMDAR is a multisubunit receptor tha glutamate by fluxing Ca^{2}. It has seve tions, which include contributing to increased functional neurons during development (neuro fects) and the synaptic plasticity associated wi and memory (e.g., the "long-term potentiation" transmission after high-frequency stimulation pus). Pathological, hyperactivation of NMD

known to lead to seizures and Ca^{2}-mediated "excitotoxicity" in neurons. In addition to the glutamate/NMDA agonist binding site, NMDARs contain several modulatory sites. These include a coagonist site for glycine (which normally may be occupied substantially under physiological conditions), proton sites that are inhibitory to channel function, and an Mg^{2} binding site that inhibits Ca^{2} flux until the membrane environment is depolarized. Polyamines also modulate the NMDAR, both positively and negatively, at several sites (see Johnson 1996; Rock and Macdonald, 1995). One site increases channel function by increasing the affinity of the glycine site for this coagonist, but whether this is physiologically important given the relatively high concentrations of glycine normally present in the CNS is unknown. Another polyamine site also increases channel function by reducing the inhibitory effects of protons on the NMDAR channel. Yet another polyamine site (or sites) inhibits channel function, in this case probably by simple steric hindrance of channel opening. These latter inhibitory effects generally require considerably higher concentrations of polyamines, and their physiological relevance is questionable as a result. Thus, although all these sites are important under experimental conditions, concerns about

when concentrations of endogenous polyamin logically high. All these conditions may coexi cohol withdrawal (see following discussion).

One of the reasons for this symposium was for therapeutic intervention with the NMDAR polyamine-sensitive sites. It is important to rec this may have advantages over other interventi NMDAR function. Thus, the physiological im NMDAR in learning and memory makes it hig able to target inhibitors at the glutamate/NMD site or the NMDAR channel itself. Inhibition here inevitably would disrupt learning and me addition, the channel-blocking drugs, such as ine, ketamine, and dizocilpine (MK801), have tial and are neurotoxic. Inhibition via the coag site offers an alternative, but if this site is clos by physiological concentrations of glycine, the here inevitably will inhibit physiological level function. Inhibition of NMDAR function by d tion with the glycine-independent polyamine s suffer from these constraints because this site i fully only when polyamine concentrations are physiologically. By using such antagonists, it

physiological importance have focused our attention on the potentiating, coagonist effects of polyamines on NMDAR function by interactions with the glycine-independent site. This can occur over the pathophysiological range of endogenous polyamine concentrations (1–100 M) and can result in approximately a 2-fold increase in Ca^{2} flux through the activated receptor. When administered directly into CNS, spermine produces severe neuronal damage, and this damage can be inhibited partially by coadministration of MK-801 (Goodenough et al., 2000; Otsuki et al., 1995). This effect of polyamines has been implicated in several pathological states, most notably NMDAR-mediated neuronal damage that occurs during anoxia and glucose deprivation, as in a cerebrovascular stroke (Carter et al., 1995).

The coagonist effects of polyamines on NMDARs have rather specific subunit requirements for the receptor complex. Thus, deletion of a specific sequence (the n-terminal "cassette") in an NR1 splice variant, the NR1-1a subunit, is associated with sensitivity to this effect of polyamines in NMDARs that have this subunit. In contrast, the presence of the n-terminal cassette in other splice variants (e.g., NR1-1b) renders the receptor insensitive to this effect of polyamines. The NR2 subunit composition also contributes to polyamine sensitivity; thus, the NR2B subunit renders an NMDAR particularly sensitive to potentiation by polyamines, whereas NR2C subunits are insensitive and NR2A subunits are intermediate (Williams et al., 1994). None of these subunits materially alters the inhibitory effects of polyamines on the NMDAR. Thus, any situation in which NMDAR subunit composition is undergoing alteration may have profound effects on the balance between activating and inhibiting effects of polyamines on the NMDAR. This will be of particular pathophysiological relevance

possible to inhibit the pathological "overactiva NMDARs while preserving physiological leve intact. Drugs that do this might be valuable du withdrawal (see following discussion) as well other disease states in which NMDAR functio cated, such as stroke and Alzheimer's disease.

Several candidate drugs are believed to inh function by interaction with the polyamine site sideration. The most studied are the drugs of tl group (which include eliprodil) that are believ allosterically with the polyamine site and that NMDAR function at least partly by this mecha lagher et al., 1996). Of particular interest to al dence is the suggestion that the "anticraving" prosate, may have a similar mechanism, althou aspect of its mechanism is very weak. Thus, lil acamprosate both inhibits polyamine binding the effects of polyamines on dizocilpine bindi NMDAR (al Qatari et al., 1998; Naassila et al. Electrophysiologically, acamprosate has been inhibit potentiating effects of polyamines on N mediated currents but only in a relatively smal of neurons and only at relatively high concentr and Lovinger, 2000). Both ifenprodil and acam seem unlikely to interact directly with polyami sites because they are structurally very dissimi amines (and to each other). However, two poly logs, arcaine and agmatine, are much better ca polyamine site inhibitors. Thus, radioligand bi suggest that these two agents act as competitiv at the activating polyamine site on the NMDA tively low concentrations (Littleton et al., 200 1997). At higher concentrations the picture is

by "agonist" interactions of arcaine and agmatine with other, inhibitory, polyamine sites. Agmatine in particular seems very worthy of further study both as a potential lead compound for drug development and because it occurs naturally in the mammalian brain, where it may be synthesized (from arginine) and released at the same time as the polyamines, spermine, and spermidine (Gilad et al., 1996). Even more intriguing, it is possible that agmatine may be converted to the polyamines under certain conditions.

may rapidly render NMDARs insensitive to eth the development of acute tolerance to ethanol et al., 1997; and see subsequent discussion). In the role of NR2 subunits, alterations in NR1 sp also may be important. Certainly, other posttra modifications, in addition to phosphorylation kinase, may play a role in determining the sens ethanol of the NMDA receptor (Anders et al., summary, there is no conclusive evidence of a

Thus, although none of these drugs is highly potent or highly specific for the polyamine site on the NMDAR, nevertheless their efficacy against specific conditions can be used to evaluate the possibility that polyamine activation of NMDARs is causally important in these conditions (see following discussion).

DISCUSSION

Ethanol is acutely inhibitory to NMDAR function at concentrations within the pharmacological range (10–100 mM). It has been suggested that in some neurons this inhibition may be mediated via the glycine coagonist site, but the evidence for this is far from conclusive. Because one of the activating sites for polyamines on the NMDAR interacts allosterically with the glycine site, it is conceivable that ethanol also could modify the glycine site negatively via a similar mechanism. However, there is no evidence for this, and ethanol is reported to be neither more nor less effective on NMDAR function in the presence of polyamines (Lovinger, 2000). By using an in vivo animal model, it has been suggested that polyamines may have an important role in modulating NMDA receptor function, and that polyamine enhancement of NMDA receptor function is relatively insensitive to the inhibitory effects of ethanol (Matsumoto et al., 1993). Regardless of whether ethanol affects polyamine function by directly altering the modulatory effects of polyamines on the receptor, the question remains whether ethanol and polyamines share common modulatory mechanisms. Thus, the inhibitory effects of ethanol on the neurotoxicity induced by polyamines and NMDA in cerebellar granule cells suggest some interaction between ethanol and the polyamine site (Liljequist et al., 2000). In addition, this question can be addressed by evaluating whether there are common subunit requirements for activation by polyamines and inhibition by ethanol. The evidence to date is inconclusive; thus, it has been suggested that ifenprodil-sensitive NMDARs are also those most sensitive to ethanol (Yang et al., 1996). This would implicate NR2B subunits in the action of ethanol, and some data suggest that those receptors which contain the NR2B subunit are indeed the most ethanol-sensitive, especially in a neuronal context (Lovinger, 2000). However, this does not always appear to be the case under other conditions. The situation is complicated by the fact that the NR2B subunit (which confers acute sensitivity to polyamines and perhaps to ethanol) also has a fyn-kinase phosphorylation site that

acute interaction between ethanol and polyami
the NMDAR protein complex, although there
similarities in the subtypes of NMDARs most
ethanol and polyamines. However, the presenc
may alter NMDAR function by indirect effects
polyamine sites, for example, by inhibiting orn
boxylase, the rate-limiting step in polyamine b
(Davidson and Wilce, 1998).

As regards the subacute and chronic effects
the NMDAR, there are several potential intera
polyamines. First, the rapid phosphorylation o
units of the NMDAR by fyn-kinase has been s
underlie the development of acute tolerance to
(Miyakawa et al., 1997). This receptor subunit
sitivity to polyamines and thus to agents that i
tor function via the polyamine site (such as ife
Interestingly, subacute exposure to ethanol is
increase the sensitivity of NMDARs to inhibit
ifenprodil (Blevins et al., 1995) and perhaps a
(al Qatari et al., 1998) which suggests that som
lational modulation may underlie this phenom
(e.g., Anders et al., 1999). Interactions betwee
and their antagonists on the NMDAR during t
ment of acute tolerance to ethanol seem to be
for study.

More chronic exposure to ethanol up-regul
numbers in some systems (e.g., Hu and Ticku,
this is not a universal finding. However, in all
NMDAR function appears to increase after ch
sure to ethanol, presumably as an adaptive res
acute inhibition of NMDAR function by ethan
surprisingly, this increase in NMDAR functio
is increased further during the early stages of e
drawal. When up-regulation in receptor numb
served, it is commonly associated with an incr
and NR2B mRNA, but with no change in total
(Hu et al., 1996). Experiments in neuronal cul
that NR1 subunit protein is up-regulated but t
consequence of increased stability of the mess
than of increased gene expression. In contrast,
in NR2B protein levels does appear to be a co
an ethanol-induced increase in gene expressio
subunit (Hu et al., 1996). There also appear to
in the relative proportion of NR1 splice varian
ing chronic ethanol exposure and during withd
acamprosate treatment also is reported to caus
rapid changes in NR1 splice variant expression

al., 1996). All of the ethanol-induced changes in NMDAR gene expression are predicted to alter polyamine sensitivity, usually in the direction of increased sensitivity to activating effects of polyamines, but this has not been rigorously investigated. Indirect evidence in support comes from the observation that binding sites for [3H]ifenprodil are increased in rat brain after chronic exposure to ethanol (Matsumoto, 2000). Interestingly, the alterations in expression of the NR2A and NR2B subunits (which may make the most difference to polyamine sensitivity during withdrawal) show sex differences (Devaud and Morrow, 1999). This suggests that there could be polyamine-mediated differences between the sexes in NMDAR activation during the alcohol withdrawal syndrome and/or sex differences in the consequences of alcohol exposure in utero (see subsequent discussion).

In addition to effects of ethanol exposure on sensitivity of the NMDAR to polyamines, chronic ethanol exposure also increases the activity of ornithine decarboxylase, the rate-limiting enzyme for polyamine synthesis (Davidson and Wilce, 1998). The same authors have reported that this increases synthesis and accumulation of the polyamines during ethanol withdrawal. Thus, during withdrawal there are increased numbers and/or increased function of polyamine-sensitive NMDARs, together with an increased concentration of endogenous polyamines. The implication is clearly that NMDARs will be overactivated pathologically by glutamate release during withdrawal, and that this effect will be accentuated by the interaction of polyamines with binding sites on the NMDAR.

The most direct evidence that polyamines are related causally to consequences of alcohol withdrawal comes from the use of the inhibitor of ornithine decarboxylase, difluoro-methyl ornithine. Difluoro-methyl ornithine, given intracerebroventricularly, effectively inhibited alcohol withdrawal seizures in vivo (Davidson and Wilce, 1998). Additionally, there was a positive correlation between ornithine decarboxylase activity and the severity of the ethanol withdrawal syndrome, and the decline in ornithine decarboxylase activity after withdrawal shared a similar time course to the withdrawal syndrome (Davidson and Wilce, 1998). Several of the other putative polyamine site modulators also have been shown to be effective inhibitors of this aspect of the alcohol withdrawal syndrome in animals. These agents include oral ifenprodil and eliprodil (Kotlinska and Liljequist, 1996); acamprosate, when given repeatedly intraperitoneally (Littleton et al., 1988); and agmatine, also given

mostly merely additive with withdrawal-induc
and enhanced polyamine toxicity was seen onl
derived from female rat neonates in the CA3 h
region (Littleton et al., 2000). Preliminary stuc
neonatal rats in vivo suggest that there also ma
differences in behavioral deficits associated wi
intermittent ethanol exposure, and on the prev
fects of polyamine antagonists on these (Barro
2000). Whether there is any connection betwe
observations remains to be investigated. These
neonatal rats emphasize once again the potenti
tance of interactions between ethanol and poly
tabolism during developmental changes in the
vous system.

SIGNIFICANCE

These results leave little doubt that polyam
plicated in both behavioral and neuropatholog
quences of alcohol withdrawal. The extent of t
ment, and whether it is important in human dis
remains to be discovered. Based on evidence f
situations in which polyamines are known to b
ically important, such as stroke, it seems likely
polyamines are released during ethanol withdr
of a cascade of excitotoxic reactions. If so, it is
that interference with this cascade will have be
sequences, both for behavior (e.g., suppressior
and for neurodegeneration. It is clearly possibl
with the cascade by using existing drugs, but a
have disadvantages that arise from nonspecific
major polyamine site involved. It is likely that
logical roles of polyamines on neurons are gre
development, and this may indicate that intera
ethanol in producing deficits associated with fi
syndrome are most important. Therapeutic inte
here will be difficult, because inhibitory effect
on "neurotrophic" polyamine effects presumab
enhanced by treatments aimed at inhibition of
effects of polyamines during periods of ethano
However, it is possible that different polyamin
involved in the separate effects, and, if so, spe
that target one or the other might be valuable.
practical use in alcohol dependence is made of
interfere with the polyamine sites on NMDAR
that the polyamines are yet another important
adaptive responses to ethanol and also are inv

intraperitoneally (Uzbay et al., 2000). In addition to their probable role in ethanol withdrawal seizures, polyamines also are predicted to potentiate NMDAR-mediated excitotoxicity that occurs during ethanol withdrawal. So far this has been studied only in vitro, in organotypic hippocampal cultures, where it has been shown that ifenprodil, acamprosate, and agmatine are effective inhibitors of ethanol withdrawal-induced toxicity (Littleton et al., 2000). Interestingly, in this in vitro model, polyamines appeared to be generating the hyperexcitation and neurotoxici company alcohol withdrawal.

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2002-2003

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seizure

<clinical sign, neurology> A sudden attack or convulsion due to involuntary electrical activity in the brain. It is due to an uncontrolled burst of electrical activity in the brain that can result in a wide variety of clinical manifestations such as: muscle twitches, staring, tongue biting, urination, loss of consciousness and total body shaking.

Examples include: focal seizure, absence seizure, partial seizure, psychomotor seizure, petit-mal seizure and grand-mal seizures.

(27 Sep 1997)

Previous: seismography, seismological, seismology, seismometer, seismoscope, seismotherapy
Next: seizure, causes of, seizures, sejunction, selachian, selachii

epilepsy

<disease, neurology> The paroxysmal transient disturbances of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances or perturbation of the autonomic nervous system.

Symptoms are due to paroxysmal disturbance of the electrical activity of the brain. On the basis of origin, epilepsy is idiopathic (cryptogenic, essential, genetic) or symptomatic (acquired, organic). On the basis of clinical and electroencephalographic phenomenon, four subdivisions are recognised:

1. Grand mal epilepsy (major epilepsy, haut mal epilepsy) subgroups: generalised, focal (localised), jacksonian (rolandic)

2. Petit mal epilepsy

3. Psychomotor epilepsy (temporal lobe epilepsy, psychic, psychic equivalent or variant) subgroups: psychomotor proper (tonic with adversive or torsion movements or masticatory phenomena), automatic (with amnesia) and sensory (hallucinations or dream states or d,j. Vu)

4. Autonomic epilepsy (diencephalic), with flushing, pallor, tachycardia, hypertension, perspiration or other visceral symptoms.

Synonym: epilepsia.

Origin: Gr. Epilepsia = seizure

(14 May 1997)

Previous: epilemmal ending, epilepidoma, epilepsia, epilepsia partialis continua
Next: epilepsy, absence, epilepsy, complex partial, epilepsy, frontal lobe

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L89 ANSWER 25 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:24432 BIOSIS
DN PREV199598038732
TI Antiepileptic effects of inhibitors of nitric oxide synthase examined in pentylenetetrazole-induced seizures in rats.
AU Osonoe, Kouichi; Mori, Norio (1); Suzuki, Katsuaki; Osonoe, Minako
CS (1) Dep. Neuropsychiatry, Fukushima Med. Coll., 1 Hikariga-oka, Fukushima-shi 960-12 Japan
SO Brain Research, (1994) Vol. 663, No. 2, pp. 338-340.
ISSN: 0006-8993.
DT Article
LA English
AB The effects of intraperitoneal N-G-methyl-**L-arginine** and N-omega-nitro-**L-arginine** methyl ester, specific inhibitors of nitric oxide (NO) synthase, were examined on the pentylenetetrazol (PTZ)-induced **seizures** in rats. The incidence and latency for the onset of myoclonic jerks, clonic **seizures**, and tonic generalized extension were observed as specific parameters among PTZ-induced seizures. Both drugs preferentially suppressed the tonic generalized extension and prolonged the latency for the onset of each parameter, suggesting NO has a significant effect on the PTZ-induced seizure.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Nervous System - Pathology *20506
Toxicology - General; Methods and Experimental *22501
BC Muridae *86375
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); **Metabolism** ; Nervous System (Neural Coordination); Toxicology
IT Chemicals & Biochemicals
NITRIC OXIDE SYNTHASE; PENTYLENETETRAZOLE; N-OMEGA-NITRO-L-ARGININE METHYL ESTER
IT Miscellaneous Descriptors
CLONIC SEIZURE; EPILEPSY; MYOCLONIC JERK; N-G-METHYL-L-ARGININE; N-OMEGA-NITRO-L-ARGININE METHYL ESTER; TONIC GENERALIZED EXTENSION
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name

L89 ANSWER 24 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1994:504458 BIOSIS
DN PREV199497517458
TI Alpha-Guanidinoglutaric acid, an endogenous convulsant, as a novel nitric oxide synthase inhibitor.
AU Yokoi, Isao (1); Kabuto, Hideaki; Habu, Hitoshi; Mori, Akitane
CS (1) Dep. Neurosci., Inst. Mol. Cell. Med., Okayama Univ. Med. Sch., 2-5-1 Shikata-cho, Okayama 700 Japan
SO Journal of Neurochemistry, (1994) Vol. 63, No. 4, pp. 1565-1567. ISSN: 0022-3042.
DT Article
LA English
AB The effects of alpha-guanidinoglutaric acid (GGA), the levels of which were increased in the cobalt-induced epileptic focus tissue in the cerebral cortex of cats, on brain nitric oxide synthase (NOS) activity were observed. GGA inhibited NOS activity in a linear mixed manner (K-i = 2.69 mu-M) and was as effective as N-G-monomethyl-L-arginine (MeArg; K-i = 3.51 MM), a well-known NOS inhibitor. Although MeArg was synthesized by substituting the guanidino nitrogen of **L-arginine** (Arg), GGA was a non-guanidino nitrogen-substituted guanidino compound. On the other hand, Arg, which is an endogenous NOS substrate, elevates the threshold of **seizures** induced by GGA. There is evidence that GGA is an endogenous, potent, and non-guanidino nitrogen-substituted NOS inhibitor and that suppression of nitric oxide biosynthesis may be involved in GGA-induced convulsions. Therefore, GGA may be a useful tool in elucidating the chemical nature of NOS and the physiological function of nitric oxide.
CC Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Enzymes - Physiological Studies *10808

L89 ANSWER 23 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:178282 BIOSIS
DN PREV199598192582
TI Dose-dependent anticonvulsant and proconvulsant effects of nitric oxide synthase inhibitors on seizure threshold in a cortical stimulation model in rats.
AU Rundfeldt, Chris; Koch, Rainer; Richter, Angelika; Mevissen, Meike; Gerecke, Uwe; Loescher, Wolfgang (1)
CS (1) Dep. Pharmacology Toxicolgoy Pharmacy, Sch. Veterinary Med., Buenteweeg 17, D-30559 Hannover Germany
SO European Journal of Pharmacology, (1995) Vol. 274, No. 1-3, pp. 73-81. ISSN: 0014-2999.
DT Article
LA English
AB In the central nervous system, nitric oxide (NO) is increasingly being considered as a trans-synaptic retrograde messenger, being involved for instance in cellular responses to stimulation of glutamate receptors of the NMDA subtype. Thus, compounds that modify NO production, such as NO synthase inhibitors, may provide a means of altering NMDA receptor function. The functional consequences of NO synthase inhibition are, however, complicated by the fact that NO not only serves as a messenger to activate guanylyl cyclase and so to raise cGMP in target cells in response to NMDA receptor stimulation but also to induce feedback inhibition of the NMDA receptor via a redox modulatory site on the receptor complex. This may explain the contrasting results obtained previously with NO synthase inhibitors in animal models of ischaemia and seizures. In the present study, we tried to resolve the reported discrepancies about the effects of NO synthase inhibitors in seizure models by studying such drugs at various doses in a novel model of cortical seizure threshold. In this model, the threshold for seizures in rats is determined at short time intervals by applying ramp-shaped electrical pulse-trains directly to the cerebral cortex, allowing one to determine the time course of anti- or proconvulsant drug effects in individual rats. Two NO synthase inhibitors, N-G-nitro-L-arginine and N-g-nitro-L-arginine methyl ester, were compared with a clinically effective antiepileptic drug, i.e. valproate. Whereas N-G-nitro-**L-arginine** methyl ester, 1-40 mg/kg i.p., did not exert any marked effects on **seizure** threshold, N-G-nitro-**L- arginine**, 1-10 mg/kg, induced significant threshold increases, which reached about 50% of the increases seen with valproate, 200 mg/kg. At 40 mg/kg N-G-nitro-**L-arginine** , however, a significant and long-lasting decrease in **seizure** threshold was observed, presumably induced by blockade of the negative feedback exerted by NO on the NMDA receptor. The data demonstrate that a NO synthase inhibitor can produce both anti- and proconvulsant effects in the same model, depending on the dose administered. Similar observations have previously been reported for NMDA receptor antagonists and clinically established antiepileptic drugs, so that the biphasic effects of NO synthase inhibitors are not unusual for drugs with anticonvulsant activity.
CC Cytology and Cytochemistry - Animal *02506
Biochemistry - Gases *10012
Biochemical Methods - Proteins, Peptides an

L89 ANSWER 22 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:182191 BIOSIS
DN PREV199598196491
TI Nitric oxide-related agents alter alcohol withdrawal in male rats.
AU Adams, Michael L. (1); Sewing, Bryan N.; Chen, Jingling; Meyer, Edward R.; Cicero, Theodore J.
CS (1) Dep. Psychiatry Washington Univ. Sch. Med., Box 8134, 4940 Chidlren's Place, St. Louis MO 63110 USA
SO Alcoholism Clinical and Experimental Research, (1995) Vol. 19, No. 1, pp. 195-199.
ISSN: 0145-6008.
DT Article
LA English
AB Evidence has been reported supporting the hypothesis that nitric oxide (NO) partially mediates the expression of morphine dependence. To examine whether NO-related agents also affect the expression of alcohol dependence, adult male rats were treated chronically with alcohol. Upon withdrawal of alcohol administration, abstinence signs were observed after treatment with a NO synthase (NOS) inhibitor, N-G-nitro-**L-arginine** methyl ester (NAME), or a NO donor, isosorbide dinitrate (ISDN). Withdrawal severity was based primarily on the presence and intensity of tremors, rigidity, hyperactivity, and spontaneous and audiogenic **convulsions**. The NOS inhibitor, NAME (10-100 mg/kg), injected during alcohol withdrawal significantly inhibited withdrawal severity decreasing the intensity of signs of hyperactivity, tremors, and rigidity, but not affecting the occurrence of convulsions. The NO donor, ISDN (30 mg/kg), administered during alcohol withdrawal significantly increased the severity of most withdrawal signs. These results suggest that NO mediates some aspects of the expression of alcohol dependence.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Metabolism - Proteins, Peptides and Amino Acids *13012
Endocrine System - Neuroendocrinology *17020
Nervous System - Pathology *20506
Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004
Toxicology - General; Methods and Experimental *22501
BC Muridae *86375
IT Major Concepts
Behavior; Endocrine System (Chemical Coordination and Homeostasis); **Metabolism**; Nervous System (Neural Coordination); Toxicology
IT Chemicals & Biochemicals
ALCOHOL
IT Miscellaneous Descriptors
ALCOHOL DEPENDENCE; HYPERACTIVITY; RIGIDITY; TREMOR
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 64-17-5 (ALCOHOL)

L89 ANSWER 20 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:475418 BIOSIS
DN PREV199699204974
TI **Anticonvulsant** effects of 7-nitroindazole in rodents with reflex **epilepsy** may result from **L-arginine** accumulation or a reduction in nitric oxide or L-citrulline formation.
AU Smith, S. E.; Man, C. M.; Yip, P. K.; Tang, E.; Chapman, A. G.; Meldrum, B. S. (1)
CS (1) Dep. Neurol., Inst. Psychiatry, De Grespigny Park, Denmark Hill, London SE5 8AF UK
SO British Journal of Pharmacology, (1996) Vol. 119, No. 1, pp. 165-173. ISSN: 0007-1188.
DT Article
LA English
AB To investigate the role of nitric oxide in epilepsy we have studied the effects of agents which affect nitric oxide synthesis in sound-induced seizures in DBA/2 mice and in genetically epilepsy-prone (GEP) rats. The neuronal selective nitric oxide synthase inhibitor, 7-nitroindazole (7-NI) is anticonvulsant in these models with ED-50 values against clonic seizures in mg kg-1 i.p. (times following injection) of: 74 (+0.25 h), 120 (+1 h) in DBA/2 mice, and 56 (+0.25 h), 42 (+0.5 h), 36 (+1 h), 28 (+2 h), 38 (+4 h), 93 (+8 h) in GEP rats. Therapeutic indices (locomotor deficit ED50/anticonvulsant ED-50) for 7-NI are low, ranging from 0.6 to 1.1 at +0.25 h to +1 h after administration in GEP rats, but are more favourable at later times (1.6 at +2 h and 2.9 at +4 h). The substrate for nitric oxide synthase, **L-arginine** (500-5000 mg kg-1, i.p. or 100-300 mu-g, i.c.v.) but not D-arginine (300 mu-g i.c.v.) is **anticonvulsant** in DBA/2 mice. **L-Arginine** (500-5000 mg kg-1, i.p. or 1800-6000 mu-g, i.c.v.) is a more potent **anticonvulsant** than D-arginine (1500-2500 mg kg-1, i.p. or 6000 mu-g, i.c.v.) in GEP rats. In DBA/2 mice, **L-arginine** (30 mu-g i.c.v.) reverses the **anticonvulsant** effect of 7-NI (50 mg kg-1, i.p.). In GEP rats, low dose **L-arginine** (25-50 mg kg-1, i.p.) but not D-arginine (50 mg kg-1, i.p.) reverses the **anticonvulsant** effect of low dose 7-NI (25 mg kg-1, i.p.). A higher dose Of **L-arginine** (500 mg kg-1, i.p.) or 7-NI (50 mg kg-1, i.p.) produces summation of **anticonvulsant** effect. The product for nitric oxide synthase, L-citrulline (250-831 mu-g i.c.v.), is **convulsant** in DBA/2 mice. The **anticonvulsant** effect of the neuronal selective nitric oxide synthase inhibitor, 7-nitroindazole, may therefore be mediated by **L-arginine** accumulation, as well as by a reduction in nitric oxide and L-citrulline formation in rodent models of reflex **epilepsy**.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General *10060
Biophysics - Membrane Phenomena *10508
Metabolism - Proteins, Peptides and Amino Acids *13012
Nervous System - Physiology and Biochemistry *20504
Nervous System - Pathology *20506
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Neuropharmacology *22024
BC Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Membranes (Cell Biology); **Metabolism**; Nervous System (Neural Coordination); Pharmacology
IT Chemicals & Biochemicals
7-NITROINDAZOLE; L-ARGININE; NITRIC OXIDE; L-CITRULLINE; NITRIC OXIDE SYNTHASE
IT Miscellaneous Descriptors
ANTICONVULSANT EFFECTS; ENZYME INHIBITOR; FORMATION; L-ARGININE; L-CITRULLINE; NERVOUS SYSTEM; NERVOUS SYSTEM DISEASE; NITRIC OXIDE; NITRIC OXIDE SYNTHASE; PHARMACODYNAMICS; PHARMACOLOGY; REFLEX EPILEPSY; SOUND-INDUCED SEIZURES; 7-NITROINDAZOLE

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 2942-42-9 (7-NITROINDAZOLE)
74-79-3 (L-ARGININE)
10102-43-9 (NITRIC OXIDE)
372-75-8 (L-CITRULLINE)
125978-95-2 (NITRIC OXIDE SYNTHASE)

L89 ANSWER 16 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:322269 BIOSIS
DN PREV199800322269
TI Intrasynaptosomal free calcium and nitric oxide **metabolism** in central nervous system oxygen toxicity.
AU Wang, W. Jun (1); Ho, X. Pin; Yan, Y. Lan; Yan, T. Hua; Li, C. Lang
CS (1) Div. Mol. Pharmacol., Naval Neurobiol. Res. Cent., Naval Med. Coll., No. 2 Ma Qun St., Nanjing 210049 China
SO Aviation Space and Environmental Medicine, (June, 1998) Vol. 69, No. 6, pp. 551-555.
ISSN: 0095-6562.
DT Article
LA English
AB Background: Central nervous system (CNS) oxygen (O2) toxicity is complex, and the etiology of its most severe manifestation, O2 **convulsions**, is yet to be determined. A role for nitric oxide (NO) has been proposed, although recent data have indicated that NO is synthesized from **L-arginine** by an enzyme, NO synthase (NOS). The enzyme is dependent on free calcium (Ca2+) concentration, therefore increases in intracellular Ca2+ may constitute the physiological and pathophysiological mechanisms for stimulating the synthesis of NO. Methods: In this study, the intrasynaptosomal free calcium concentration ((Ca2+)i) was measured by the fluorescence of fura-2/AM, and cGMP (as an indirect marker of NO levels) was by radioimmunoassay (RIA) in the rat hippocampus after hyperbaric oxygen (HBO) exposure. We also investigated the effects of daurisoline (DSL, calcium channel blocker) and N-nitro-L-arginine (LNNA, NOS inhibitor) on the above biochemical parameters and the development of oxygen toxicity. Results: The results show that when the rats were exposed to HBO at 0.5 MPa the intrasynaptosomal Ca2+ and cGMP levels increased by two and three times, respectively, whereas with the use of DSL prior to HBO, the accumulation of (Ca2+)i and cGMP dropped to 56% and 60%, correspondingly. In the rats medicated with LNNA prior to HBO. (Ca2+)i and cGMP levels dropped to 70% and 36% of the HBO group. At the same time, the appearance of CNS oxygen toxicity was delayed and the survival rate increased. The protective effects of LNNA were reversed by L-arginine pretreatment. These findings suggest that the neuronal Ca2+ overload during HBO exposure is a major factor in the pathogenesis of CNS O2 toxicity, and cGMP-NO pathways may be directly involved in HBO-induced seizures.
CC Nervous System - General; Methods *20501
Cytology and Cytochemistry - Animal *02506
Radiation - General *06502
Biochemical Studies - General *10060
Biophysics - General Biophysical Studies *10502
Enzymes - General and Comparative Studies; Coenzymes *10802
Metabolism - General Metabolism; Metabolic Pathways *13002
Endocrine System - General *17002
Toxicology - General; Methods and Experimental *22501
Immunology and Immunochemistry - General; Methods *34502
BC Muridae 86375
IT Major Concepts
Biochemistry and Molecular Biophysics; **Metabolism**; Nervous System (Neural Coordination); Toxicology
IT Parts, Structures, & Systems of Organisms
hippocampus: nervous system
IT Diseases
central nervous system oxygen toxicity: nervous system disease, toxicity, pathogenesis
IT Chemicals & Biochemicals
calcium ion: free, intrasynaptosomal; cyclic AMP: nitric oxide marker; daurisoline: calcium channel blocker; nitric oxide: hippocampal **metabolism**, synthesis; oxygen: hyperbaric exposure; N-nitro-L-arginine: enzyme inhibitor

IT Methods & Equipment
fura-2-AM fluorescence: analytical method; radioimmunoassay: analytical method
IT Miscellaneous Descriptors
seizure
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Sprague-Dawley rat (Muridae): adult, male, young
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 7440-70-2 (CALCIUM)
10102-43-9 (NITRIC OXIDE)
7782-44-7 (OXYGEN)
14127-61-8 (CALCIUM ION)

L89 ANSWER 15 OF 75 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:306688 BIOSIS
DN PREV199900306688
TI Independent and combined effects of **L-arginine** and diazepam on ammonium chloride-induced **convulsions** in rats.
AU Paul, Vanaja (1); Jayakumar, A. R.
CS (1) Department of Pharmacology and Environmental Toxicology, Dr. A.L.M. Postgraduate Institute of Basic Medical Sciences, University of Madras, Taramani, Chennai, 600 113 India
SO Indian Journal of Physiology and Pharmacology, (April, 1999) Vol. 43, No. 2, pp. 199-204.
ISSN: 0019-5499.
DT Article
LA English
SL English
AB The independent and combined effects of **L-arginine** (840 mg/kg) and diazepam (0.75 mg/kg) pretreatment (30 min) were tested on ammonium chloride (400 mg/kg) - induced **convulsions** in rats. Ammonia concentrations were determined in blood and brain regions (cerebral cortex, brain stem and cerebellum) 30 min after **L-arginine** or diazepam treatment. Ammonia concentrations were measured at the time of induction of **convulsions** by ammonium chloride in **L-arginine**, diazepam or saline pretreated animals. **L-arginine** and not diazepam decreased ammonia concentrations in control as well as in ammonium chloride-treated animals. However, both the compounds suppressed **convulsions** elicited by ammonium chloride. Protection produced concurrently by these agents was much greater than that produced by them independently. It is concluded that convulsions caused by hyperammonemic condition can be suppressed either by preventing a rise in brain ammonia to toxic level or by anticonvulsant agents having a GABA potentiating action. A much greater protection can be achieved if agents having these properties are administered concurrently.
CC Pharmacology - General *22002
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Metabolic Disorders *13020
Toxicology - General; Methods and Experimental *22501
Nervous System - General; Methods *20501
BC Muridae 86375
IT Major Concepts
Metabolism; Neurology (Human Medicine, Medical Sciences); Pharmacology
IT Diseases
convulsion: nervous system disease, toxicity; hyperammonemia: **metabolic** disease
IT Chemicals & Biochemicals
ammonium chloride: epileptogen, neurotoxin; diazepam: anticonvulsant - drug, neuroprotectant - drug; **L-arginine**: **anticonvulsant** - drug, **metabolic** - drug, neuroprotectant - drug
IT Miscellaneous Descriptors
combined drug effects
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 74-79-3 (L-ARGININE)
439-14-5 (DIAZEPAM)
12125-02-9 (AMMONIUM CHLORIDE)

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L1              1 S AGMATINE/CN
L2              0 S BIOSIS, MEDLINE , CAPLUS, USPATFUL

      FILE 'HOME' ENTERED AT 19:53:31 ON 07 SEP 2003

      FILE 'BIOSIS, MEDLINE, CAPLUS, USPATFULL' ENTERED AT 19:55:41 ON 07 SEP
      2003
L3            555 FILE BIOSIS
L4            275 FILE MEDLINE
L5            936 FILE CAPLUS
L6             49 FILE USPATFULL
      TOTAL FOR ALL FILES
L7           1815 S L1
L8              0 FILE BIOSIS
L9              0 FILE MEDLINE
L10             0 FILE CAPLUS
L11             0 FILE USPATFULL
      TOTAL FOR ALL FILES
L12             0 S L2
L13           909 FILE BIOSIS
L14           544 FILE MEDLINE
L15          1383 FILE CAPLUS
L16           274 FILE USPATFULL
      TOTAL FOR ALL FILES
L17          3110 S AGMATINE
L18           909 FILE BIOSIS
L19           544 FILE MEDLINE
L20          1485 FILE CAPLUS
L21           282 FILE USPATFULL
      TOTAL FOR ALL FILES
L22          3220 S L7 OR L17
L23             3 FILE BIOSIS
L24             3 FILE MEDLINE
L25             7 FILE CAPLUS
L26            12 FILE USPATFULL
      TOTAL FOR ALL FILES
L27            25 S L22 AND (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? OR

      FILE 'STNGUIDE' ENTERED AT 20:12:21 ON 07 SEP 2003

      FILE 'USPATFULL' ENTERED AT 20:22:38 ON 07 SEP 2003

      FILE 'STNGUIDE' ENTERED AT 20:22:40 ON 07 SEP 2003
                SAVE ALL L09881215/L

      FILE 'USPATFULL' ENTERED AT 20:43:34 ON 07 SEP 2003

      FILE 'STNGUIDE' ENTERED AT 20:43:35 ON 07 SEP 2003

      FILE 'USPATFULL' ENTERED AT 20:56:00 ON 07 SEP 2003

      FILE 'STNGUIDE' ENTERED AT 20:56:02 ON 07 SEP 2003
L28             0 S L-ARGININE OR PUTRESCINE

      FILE 'BIOSIS, MEDLINE, CAPLUS, USPATFULL' ENTERED AT 21:01:37 ON 07 SEP
      2003
L29         33193 FILE BIOSIS
L30         24221 FILE MEDLINE
L31         43142 FILE CAPLUS
L32          7194 FILE USPATFULL
      TOTAL FOR ALL FILES
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L33      107750 S L-ARGININE OR PUTRESCINE
L34         191 FILE BIOSIS
L35         145 FILE MEDLINE
L36         162 FILE CAPLUS
L37          25 FILE USPATFULL
     TOTAL FOR ALL FILES
L38         523 S L33 (1S) (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? OR
L39         142 FILE BIOSIS
L40         102 FILE MEDLINE
L41         124 FILE CAPLUS
L42           9 FILE USPATFULL
     TOTAL FOR ALL FILES
L43         377 S L33 (30A) (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? O
L44         172 DUP REM L39-L41 (196 DUPLICATES REMOVED)
L45         142 S L44
L46           6 FILE BIOSIS
L47          11 S L44
L48           0 FILE MEDLINE
L49          19 S L44
L50           0 FILE CAPLUS
L51           0 S L44
L52           0 FILE USPATFULL
     TOTAL FOR ALL FILES
L53           6 S L44 AND METABOLITE
L54       25146 FILE BIOSIS
L55       18965 FILE MEDLINE
L56       33497 FILE CAPLUS
L57        6125 FILE USPATFULL
     TOTAL FOR ALL FILES
L58       83733 S L-ARGININE
L59         111 FILE BIOSIS
L60          84 FILE MEDLINE
L61          95 FILE CAPLUS
L62           9 FILE USPATFULL
     TOTAL FOR ALL FILES
L63         299 S L58 (30A) (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? O
L64           1 FILE BIOSIS
L65           0 FILE MEDLINE
L66           0 FILE CAPLUS
L67           0 FILE USPATFULL
     TOTAL FOR ALL FILES
L68           1 S L63 (2S) ACTIVE METABOLITE
L69         131 FILE BIOSIS
L70          96 FILE MEDLINE
L71         111 FILE CAPLUS
L72           9 FILE USPATFULL
     TOTAL FOR ALL FILES
L73         347 S L58 (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L74           0 FILE BIOSIS
L75          93 FILE MEDLINE
L76          98 FILE CAPLUS
L77           0 FILE USPATFULL
     TOTAL FOR ALL FILES
L78         191 S L58/AB (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS
L79           0 FILE BIOSIS
L80           0 FILE MEDLINE
L81           0 FILE CAPLUS
L82           0 FILE USPATFULL
     TOTAL FOR ALL FILES
L83           0 S L58/ABS (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVUL
L84          26 FILE BIOSIS
L85          46 FILE MEDLINE
L86          14 FILE CAPLUS
L87           8 FILE USPATFULL
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      TOTAL FOR ALL FILES
L88           94 S L73 AND (METAB?)
L89           75 DUP REM L84-L87 (19 DUPLICATES REMOVED)
L90          128 FILE BIOSIS
L91           80 FILE MEDLINE
L92          287 FILE CAPLUS
L93          349 FILE USPATFULL
      TOTAL FOR ALL FILES
L94          844 S L-ARGININE AND PUTRESCINE
L95            0 FILE BIOSIS
L96            0 FILE MEDLINE
L97            0 FILE CAPLUS
L98          156 FILE USPATFULL
      TOTAL FOR ALL FILES
L99          156 S L94 (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L100           0 FILE BIOSIS
L101           0 FILE MEDLINE
L102           0 FILE CAPLUS
L103         156 FILE USPATFULL
      TOTAL FOR ALL FILES
L104         156 S L94 AND (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? OR
L105         127 FILE BIOSIS
L106          59 FILE MEDLINE
L107         111 FILE CAPLUS
L108         287 FILE USPATFULL
      TOTAL FOR ALL FILES
L109         584 S L-ARGININE (1S) PUTRESCINE
L110           0 FILE BIOSIS
L111           0 FILE MEDLINE
L112           0 FILE CAPLUS
L113           0 FILE USPATFULL
      TOTAL FOR ALL FILES
L114           0 S L109 (3S) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L115           0 FILE BIOSIS
L116           0 FILE MEDLINE
L117           0 FILE CAPLUS
L118         153 FILE USPATFULL
      TOTAL FOR ALL FILES
L119         153 S L109 AND (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? OR
L120           0 FILE BIOSIS
L121           0 FILE MEDLINE
L122           0 FILE CAPLUS
L123           0 FILE USPATFULL
      TOTAL FOR ALL FILES
L124           0 S L109 (10S)(SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L125           0 FILE BIOSIS
L126           0 FILE MEDLINE
L127           0 FILE CAPLUS
L128         153 FILE USPATFULL
      TOTAL FOR ALL FILES
L129         153 S L109 (500A)(SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS?
                 SAVE ALL L09881215/L
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      FILE 'REGISTRY' ENTERED AT 19:52:39 ON 07 SEP 2003
L1              1 S AGMATINE/CN
L2              0 S BIOSIS, MEDLINE , CAPLUS, USPATFUL

      FILE 'HOME' ENTERED AT 19:53:31 ON 07 SEP 2003

      FILE 'BIOSIS, MEDLINE, CAPLUS, USPATFULL' ENTERED AT 19:55:41 ON 07 SEP
      2003
L3            555 FILE BIOSIS
L4            275 FILE MEDLINE
L5            936 FILE CAPLUS
L6             49 FILE USPATFULL
      TOTAL FOR ALL FILES
L7           1815 S L1
L8              0 FILE BIOSIS
L9              0 FILE MEDLINE
L10             0 FILE CAPLUS
L11             0 FILE USPATFULL
      TOTAL FOR ALL FILES
L12             0 S L2
L13           909 FILE BIOSIS
L14           544 FILE MEDLINE
L15          1383 FILE CAPLUS
L16           274 FILE USPATFULL
      TOTAL FOR ALL FILES
L17          3110 S AGMATINE
L18           909 FILE BIOSIS
L19           544 FILE MEDLINE
L20          1485 FILE CAPLUS
L21           282 FILE USPATFULL
      TOTAL FOR ALL FILES
L22          3220 S L7 OR L17
L23             3 FILE BIOSIS
L24             3 FILE MEDLINE
L25             7 FILE CAPLUS
L26            12 FILE USPATFULL
      TOTAL FOR ALL FILES
L27            25 S L22 AND (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? OR

      FILE 'STNGUIDE' ENTERED AT 20:12:21 ON 07 SEP 2003

      FILE 'USPATFULL' ENTERED AT 20:22:38 ON 07 SEP 2003

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                SAVE ALL L09881215/L

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      FILE 'STNGUIDE' ENTERED AT 20:43:35 ON 07 SEP 2003

      FILE 'USPATFULL' ENTERED AT 20:56:00 ON 07 SEP 2003

      FILE 'STNGUIDE' ENTERED AT 20:56:02 ON 07 SEP 2003
L28             0 S L-ARGININE OR PUTRESCINE

      FILE 'BIOSIS, MEDLINE, CAPLUS, USPATFULL' ENTERED AT 21:01:37 ON 07 SEP
      2003
L29         33193 FILE BIOSIS
L30         24221 FILE MEDLINE
L31         43142 FILE CAPLUS
L32          7194 FILE USPATFULL
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TOTAL FOR ALL FILES
L33 107750 S L-ARGININE OR PUTRESCINE
L34 191 FILE BIOSIS
L35 145 FILE MEDLINE
L36 162 FILE CAPLUS
L37 25 FILE USPATFULL
TOTAL FOR ALL FILES
L38 523 S L33 (1S) (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? OR
L39 142 FILE BIOSIS
L40 102 FILE MEDLINE
L41 124 FILE CAPLUS
L42 9 FILE USPATFULL
TOTAL FOR ALL FILES
L43 377 S L33 (30A) (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? O
L44 172 DUP REM L39-L41 (196 DUPLICATES REMOVED)
L45 142 S L44
L46 6 FILE BIOSIS
L47 11 S L44
L48 0 FILE MEDLINE
L49 19 S L44
L50 0 FILE CAPLUS
L51 0 S L44
L52 0 FILE USPATFULL
TOTAL FOR ALL FILES
L53 6 S L44 AND METABOLITE
L54 25146 FILE BIOSIS
L55 18965 FILE MEDLINE
L56 33497 FILE CAPLUS
L57 6125 FILE USPATFULL
TOTAL FOR ALL FILES
L58 83733 S L-ARGININE
L59 111 FILE BIOSIS
L60 84 FILE MEDLINE
L61 95 FILE CAPLUS
L62 9 FILE USPATFULL
TOTAL FOR ALL FILES
L63 299 S L58 (30A) (SEIZURE OR EPILEP? OT ANTICONVULSANT OR CONVULS? O
L64 1 FILE BIOSIS
L65 0 FILE MEDLINE
L66 0 FILE CAPLUS
L67 0 FILE USPATFULL
TOTAL FOR ALL FILES
L68 1 S L63 (2S) ACTIVE METABOLITE
L69 131 FILE BIOSIS
L70 96 FILE MEDLINE
L71 111 FILE CAPLUS
L72 9 FILE USPATFULL
TOTAL FOR ALL FILES
L73 347 S L58 (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L74 0 FILE BIOSIS
L75 93 FILE MEDLINE
L76 98 FILE CAPLUS
L77 0 FILE USPATFULL
TOTAL FOR ALL FILES
L78 191 S L58/AB (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS
L79 0 FILE BIOSIS
L80 0 FILE MEDLINE
L81 0 FILE CAPLUS
L82 0 FILE USPATFULL
TOTAL FOR ALL FILES
L83 0 S L58/ABS (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVUL
L84 26 FILE BIOSIS
L85 46 FILE MEDLINE
L86 14 FILE CAPLUS

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L87             8 FILE USPATFULL
     TOTAL FOR ALL FILES
L88            94 S L73 AND (METAB?)
L89            75 DUP REM L84-L87 (19 DUPLICATES REMOVED)
L90           128 FILE BIOSIS
L91            80 FILE MEDLINE
L92           287 FILE CAPLUS
L93           349 FILE USPATFULL
     TOTAL FOR ALL FILES
L94           844 S L-ARGININE AND PUTRESCINE
L95             0 FILE BIOSIS
L96             0 FILE MEDLINE
L97             0 FILE CAPLUS
L98           156 FILE USPATFULL
     TOTAL FOR ALL FILES
L99           156 S L94 (30A) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L100            0 FILE BIOSIS
L101            0 FILE MEDLINE
L102            0 FILE CAPLUS
L103          156 FILE USPATFULL
     TOTAL FOR ALL FILES
L104          156 S L94 AND (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? OR
L105          127 FILE BIOSIS
L106           59 FILE MEDLINE
L107          111 FILE CAPLUS
L108          287 FILE USPATFULL
     TOTAL FOR ALL FILES
L109          584 S L-ARGININE (1S) PUTRESCINE
L110            0 FILE BIOSIS
L111            0 FILE MEDLINE
L112            0 FILE CAPLUS
L113            0 FILE USPATFULL
     TOTAL FOR ALL FILES
L114            0 S L109 (3S) (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L115            0 FILE BIOSIS
L116            0 FILE MEDLINE
L117            0 FILE CAPLUS
L118          153 FILE USPATFULL
     TOTAL FOR ALL FILES
L119          153 S L109 AND (SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? OR
L120            0 FILE BIOSIS
L121            0 FILE MEDLINE
L122            0 FILE CAPLUS
L123            0 FILE USPATFULL
     TOTAL FOR ALL FILES
L124            0 S L109 (10S)(SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS? O
L125            0 FILE BIOSIS
L126            0 FILE MEDLINE
L127            0 FILE CAPLUS
L128          153 FILE USPATFULL
     TOTAL FOR ALL FILES
L129          153 S L109 (500A)(SEIZURE OR EPILEP? OR ANTICONVULSANT OR CONVULS?
                SAVE ALL L09881215/L

=>
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L5 ANSWER 4 OF 4 USPATFULL on STN

SUMM A disadvantage of this known method is that it produces usable results only when the evoked potentials are high enough in magnitude to contrast in a clearly recognizable fashion with the noise level. This generally requires a relatively large number of stimuli to provide a large enough base for the averaging techniques. This renders this known method unsuitable for **identifying** spontaneous events such as occur, for example, in an epileptic **seizure**. It is known that the spontaneous events associated with an epileptic **seizure** can be identified in the **electroencephalogram** (EEG) as characteristic patterns, referred to as "spike and wave complexes," having a duration of about 200 through 500 ms. These signal patterns are also identifiable between acute **seizures**, however, with a very different frequency from patient to patient. In extreme cases, such signal patterns can appear every second, or only once a week. As a result of the low signal-to-noise ratio, such interictal signal patterns in the EEG are usually very difficult to recognize, and then only by experienced neurologists. Such signals are virtually unrecognizable with the naked eye in the magnetoencephalogram (MEG). The point of origin of such spontaneously appearing single patterns is interpreted as an epileptogenous seat. The goal of the interpretation of an EEG or MEG in **epilepsy** diagnostics is to localize the location of this seat as exactly as possible. It is also of significance for the neurologist to obtain information regarding the spatial propagation of signal-forming, electrical excitations, both within a signal pattern and in successive, different signal patterns. Such information has heretofore only been able to be obtained using invasive techniques, such as EEG depth electrodes. Even these invasive techniques yield only a limited amount of information. Moreover, a time-resolving localization is difficult or impossible to achieve because, due to the low signal-to-noise ratio, a localization having the required precision cannot be obtained based on a single signal event, and usually a sufficient number of such events is not available for a reliable averaging.

ACCESSION NUMBER:	90:92331 USPATFULL
TITLE:	Arrangement for analyzing local bioelectric currents in biological tissue complexes
INVENTOR(S):	Abraham-Fuchs, Klaus, Erlangen, Germany, Federal Republic of Roehrlein, Gerhard, Hoechstadt, Germany, Federal Republic of Schneider, Siegfried, Erlangen, Germany, Federal Republic of
PATENT ASSIGNEE(S):	Siemens Aktiengesellschaft, Berlin and Munich, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4974602		19901204	
APPLICATION INFO.:	US 1989-393895		19890815	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1988-3827799	19880816

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Jaworski, Francis
ASSISTANT EXAMINER:	Manuel, George
LEGAL REPRESENTATIVE:	Hill, Van Santen, Steadman & Simpson
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT:	501

Behavioural Brain Research

Volume (issue): 107 (1-2) 1999

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Sort Order: Authors | Page | Title
Display style: Bibliographic | Paper

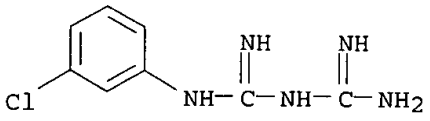
Behavioural Brain Research

Volume (issue): 107 (1-2) 1999

Previous issue | Issue Listing | Next issue

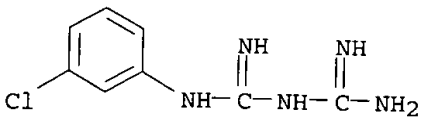
Sort Order: Authors | Page | Title
Display style: Bibliographic | Paper

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:376495 CAPLUS
DN 127:93671
TI Effects of the 5-HT3 receptor agonist 1-(m-chlorophenyl)-biguanide in the rat kindling model of **epilepsy**
AU Wada, Yuji; Shiraishi, Jun; Nakamura, Mitsuhiko; Koshino, Yoshifumi
CS Department of Neuropsychiatry, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa, 920, Japan
SO Brain Research (1997), 759(2), 313-316
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB This study assessed the action of the serotonin3 (5-HT3) receptor agonist, 1-(m-chlorophenyl)-biguanide (m-CPBG), against both kindled seizures and kindling development from the rat amygdala (AM). The intracerebroventricular (i.c.v.) administration of 40 .mu.g m-CPBG significantly increased the duration of afterdischarge and bilateral forelimb clonus of generalized kindled seizures. In addn., daily i.c.v. treatment with m-CPBG at the same dose prior to each elec. stimulation to the AM significantly facilitated behavioral and electrog. seizure development and reduced the no. of stimulations needed to elicit generalized seizures. The present results indicate that m-CPBG increases the duration of fully kindled seizures and facilitates the developmental seizure process, suggesting an excitatory role of 5-HT3 receptors in the kindling model of **epilepsy**.
ST serotonin receptor excitatory role **epilepsy** model
IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(5-HT3; effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
IT 5-HT agonists
Epilepsy
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
IT **92503-73-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
IT **92503-73-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
RN 92503-73-6 CAPLUS
CN Imidodicarbonimidic diamide, N-(3-chlorophenyl)-, hydrochloride (9CI) (CA INDEX NAME)



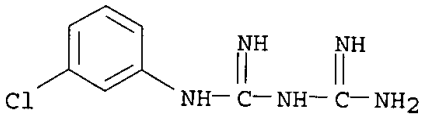
x HCl

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:376495 CAPLUS
DN 127:93671
TI Effects of the 5-HT3 receptor agonist 1-(m-chlorophenyl)-biguanide in the rat kindling model of **epilepsy**
AU Wada, Yuji; Shiraishi, Jun; Nakamura, Mitsuhiko; Koshino, Yoshifumi
CS Department of Neuropsychiatry, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa, 920, Japan
SO Brain Research (1997), 759(2), 313-316
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB This study assessed the action of the serotonin3 (5-HT3) receptor agonist, 1-(m-chlorophenyl)-biguanide (m-CPBG), against both kindled seizures and kindling development from the rat amygdala (AM). The intracerebroventricular (i.c.v.) administration of 40 .mu.g m-CPBG significantly increased the duration of afterdischarge and bilateral forelimb clonus of generalized kindled seizures. In addn., daily i.c.v. treatment with m-CPBG at the same dose prior to each elec. stimulation to the AM significantly facilitated behavioral and electrog. seizure development and reduced the no. of stimulations needed to elicit generalized seizures. The present results indicate that m-CPBG increases the duration of fully kindled seizures and facilitates the developmental seizure process, suggesting an excitatory role of 5-HT3 receptors in the kindling model of **epilepsy**.
ST serotonin receptor excitatory role **epilepsy** model
IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(5-HT3; effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
IT 5-HT agonists
Epilepsy
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
IT **92503-73-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
IT **92503-73-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 5-HT3 receptor agonist (chlorophenyl)biguanide in kindling model of **epilepsy**)
RN 92503-73-6 CAPLUS
CN Imidodicarbonimidic diamide, N-(3-chlorophenyl)-, hydrochloride (9CI) (CA INDEX NAME)



x HCl

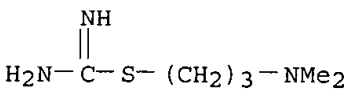
L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN **92503-73-6** REGISTRY
CN Imidodicarbonimidic diamide, N-(3-chlorophenyl)-, hydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Biguanide, 1-(m-chlorophenyl)-, hydrochloride (7CI)
OTHER NAMES:
CN 1-m-Chlorophenyl biguanide
CN mCPBG hydrochloride
MF C8 H10 Cl N5 . x Cl H
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)
CRN (48144-44-1)



● x HCl

37 REFERENCES IN FILE CA (1937 TO DATE)
37 REFERENCES IN FILE CAPLUS (1937 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 65119-89-3 REGISTRY
CN Carbamimidothioic acid, 3-(dimethylamino)propyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pseudourea, 2-[3-(dimethylamino)propyl]-2-thio- (7CI)
OTHER NAMES:
CN **Dimaprit**
FS 3D CONCORD
MF C6 H15 N3 S
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, DDFU, DRUGU, EMBASE, IPA, MEDLINE, PHAR, PROMT, RTECS*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

366 REFERENCES IN FILE CA (1937 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
366 REFERENCES IN FILE CAPLUS (1937 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

ed is:

1. A method for treating neuropathic pain, the method comprising administering an effective amount of **agmatine** to an individual in need thereof.

2. The method of claim 1 wherein the **agmatine** is administered intrathecally.

3. The method of claim 1 wherein the **agmatine** is administrated in a dosage range of approximately 0.03-10 mg.

4. The method of claim 3 wherein the **agmatine** is administrated in an approximate dose of 0.82 mg.

5. The method of claim 1 wherein the **agmatine** is formed into a suspension, a solution, or an emulsion prior to administration.

6. The method of claim 1 wherein the **agmatine** is mixed with suspending agents, stabilizing agents, dispersing agents, or combinations thereof prior to administration.

IT **306-60-5**, Agmatine
(agmatine for neuropathic pain treatment)

ACCESSION NUMBER: 2000:157468 USPATFULL
TITLE: **Agmatine** as a treatment for neuropathic pain
INVENTOR(S): Fairbanks, Carolyn A., 620 Colombia Ct., NE., Rochester, MN, United States 55906
Wilcox, George L., 2560 Kyle Ave. N., Minneapolis, MN, United States 55422
Schreiber, Kristin, 12915 N. Thomas Dr., Mequon, WI, United States 53097
Laughlin, Tinna Marie, 3800 Rum River Dr., Anoka, MN, United States 55303

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6150419		20001121
APPLICATION INFO.:	US 2000-502202		20000210 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 1998-US17033, filed on 17 Aug 1998

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-55847P	19970815 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Krass, Frederick
LEGAL REPRESENTATIVE: Kinney & Lange, P.A.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 627
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

he like are examples of C-terminal blocking groups. Amino acid analogues lacking the carboxyl functionality are also useful C-terminal blocking groups such as **agmatine**. Further, it will be appreciated that the free amino and carboxyl groups at the termini can be removed altogether from the bicyclic peptide to yield desamino and descarboxylated forms thereof without e on peptide activity.

DETD Kindling is a phenomenon in which repeated low-intensity (subconvulsive) electrical stimulation of forebrain areas leads to a progressive and permanent amplification of **seizure** activity, and is, thus, widely accepted as a model for human temporal lobe epilepsy. The effect of the present neurotrophin-derived peptides on kindling was determined as follows.

DETD Following a three-day recovery, the kindling stimulations were started. The animals received a one-second train of one-millisecond pulses at a frequency of 60 Hz and a pulse intensity of 200-400 .mu.A. These pulses were sufficient to trigger an epileptiform afterdischarge (AD) following each stimulation. Each animal was stimulated in this fashion twice a day over a period of 11 days. Progression of kindling was monitored behaviorally and electrophysiologically by recording the behavioral **seizure** stages and the duration and magnitude of afterdischarges. Fully kindled animals exhibited three consecutive stage-5 **seizures** (Racine, Electroencephalogr. Clin. Neurophysiol., 32:281 (1972)).

DETD The number of stimulations to reach stage-5 **seizures** for control rats and rats receiving the linear, cyclic and bicyclic peptides is illustrated graphically in FIG. 4. The results illustrate that the bicyclic peptide has a potency which is approximately equal to that of the anti-NGF IgG in delaying the onset of kindling in comparison to the control serum IgG, linear peptide and cyclic peptide.

DETD Although Zn.sup.2+ and neurotrophins have been implicated in the pathogenesis of neurological disease states, such as stroke (Koh, J.-Y. et al. The role of zinc in selective neuronal death after global cerebral ischemia. Science 272, 1013-1016 (1996))., Alzheimer's disease (Rylett, R. J. & Williams, L. R. Role of neurotrophins in cholinergic-neurone function in the adult and aged CNS. Trends Neurosci. 17, 490 (1994)), epilepsy (Ben-Ari, Y. & Represa, A. Brief **seizure** episodes induce long-term potentiation and mossy fiber sprouting in the hippocampus. Trends Neurosci. 13, 312-318 (1990); Rashid, K. et al. A nerve growth factor peptide retards **seizure** development and inhibits neuronal sprouting in a rat model of epilepsy. Proc. Natl. Acad. Sci. USA 92, 9495-9499 (1995)), Zn.sup.2+ inactivation of neurotrophins may mitigate neural cell death via a p75.sup.NTR mediated signal (Frade, J. M., Rodriguez-Tebar, A. & Barde, Y.-A. Induction of cell death by endogenous nerve growth factor through its p75 receptor. Nature 383, 166-168 (1996), Casaccia-Bonnefil, P., Carter, B. D., Dobrowsky, R. T. & Chao, M. V. Death of oligodendrocytes mediated by the interation of nerve growth factor with its receptor p75. Nature 383, 716-719 (1996), and Van der Zee, C. E. E. M., Ross, G. M., Riopelle, R. J. & Hagg, T. Survival of cholinergic forebrain neurons in developing p75.sup.NGFR deficient mice. Science 274, 1729-1732 (1996)) under specfic conditions. Further, in cases where activity appears to have detrimental effects (pain, inflammation (Lewin, G. R. & Mendell, L. M. Nerve growth factor and nociception. Trends Neurosci. 16, 353-359 (1993); Woolf, C. J. & Doubell, T. A. The pathophysiology of chronic pain--increased sensitivity to low threshold A.beta.-fiber inputs. Curr. Opin. Neurbiol. 4, 525-534 (1994); McMahon, S. B., Bennett, D. L. H., Priestley, J. V. & Shelton, D. L. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-IgG fusion molecule. Nature Med. 1, 774-780 (1994)), cell deaths, inhibition of neurotrophin activity using similar approaches are contemplated to have therapeutic utility.

ACCESSION NUMBER: 2001:158079 USPATFULL

TITLE: Methods of screening for factors that disrupt

neurotrophin conformation and reduce neurotrophin biological activity

INVENTOR(S): Riopelle, Richard J., Kingston, Canada
Ross, Gregory M., Kingston, Canada
Dory, Magdalena I., Rhisnes, Belgium
Weaver, Donald F., Kingston, Canada
Shamovsky, Igor L., Kingston, Canada
PATENT ASSIGNEE(S): Queen's University at Kingston, Kingston, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6291247	B1	20010918
APPLICATION INFO.:	US 1997-853910		19970509 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-241462, filed on 11 May 1994, now abandoned Continuation-in-part of Ser. No. US 1996-745608, filed on 8 Nov 1996, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	CA 1996-2190296	19961112

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Kunz, Gary L.
ASSISTANT EXAMINER: Gucker, Stephen
LEGAL REPRESENTATIVE: Steeg, Carol Miernicki, Schumacher, Lynn C.Dowell & Dowell, P.C.
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 31 Drawing Figure(s); 26 Drawing Page(s)
LINE COUNT: 2529
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 6 OF 25 MEDLINE on STN
AN 2000092320 MEDLINE
DN 20092320 PubMed ID: 10628739
TI Effects of **agmatine** on ethanol withdrawal syndrome in rats.
AU Uzbay I T; Yesilyurt O; Celik T; Ergun H; Isimer A
CS Department of Medical Pharmacology, Faculty of Medicine, Gulhane Military Medical Academy, Ankara, Turkey.. tuzbay@obs.gata.edu.tr
SO BEHAVIOURAL BRAIN RESEARCH, (2000 Jan) 107 (1-2) 153-9.
Journal code: 8004872. ISSN: 0166-4328.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000131
AB Effects of **agmatine**, which is an endogenous polyamine metabolite formed by decarboxylation of L-arginine, have been investigated on the ethanol withdrawal syndrome in rats. Adult male Wistar rats were used in the study. Ethanol (7.2% v/v) was given to the rats by a liquid diet for 21 days. **Agmatine** (20, 40, 80 and 160 mg/kg) and saline were injected to rats intraperitoneally 30 min before ethanol withdrawal testing. After 30th min, 2nd and 6th h of ethanol withdrawal, rats were observed for 5 min, and withdrawal signs which included locomotor hyperactivity, agitation, stereotyped behavior, wet dog shakes and tremor were recorded or rated. A second series of injections was given at 6 h after the first one, and subjects were then tested for audiogenic **seizures**. **Agmatine** caused dose-dependent and significant inhibitory effects on stereotyped behaviors, wet dog shakes and tremors during the observation period. It did not cause any significant change in motor coordination of naive (not ethanol-dependent) rats. Our results suggest that **agmatine** attenuates withdrawal syndrome in ethanol-dependent rats; thus, this drug may be beneficial in the treatment of ethanol dependence.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
***Agmatine: PD, pharmacology**
*Alcohol Withdrawal Delirium: PP, physiopathology
***Alcohol Withdrawal Seizures: PP, physiopathology**
Arousal: DE, drug effects
Dose-Response Relationship, Drug
Injections, Intraperitoneal
Locomotion: DE, drug effects
Rats
Rats, Wistar
Stereotyped Behavior: DE, drug effects
RN **306-60-5 (Agmatine)**

The biosyntheses of putrescine, spermidine and spermine are interrelated. Putrescine is the decarboxylation product of ornithine, catalyzed by ornithine decarboxylase. Putrescine formation may also occur by decarboxylation of arginine to form **agmatine** which is hydrolyzed to give putrescine and urea. Arginine is also involved in ornithine formation by action of the enzyme arginase. Activation of methionine by S-adenosylmethionine synthetase forms S-adenosylmethionine which is decarboxylated, after which the propylamine moiety of activated methionine may be transferred to putrescine to form spermidine and to spermidine to form spermine. Hence, putrescine serves as a precursor to spermidine and spermine and additionally has been shown to have a marked regulatory effect upon the polyamine biosynthetic pathway in that it has been shown that increased synthesis of putrescine is the first indication that a tissue will undergo renewed growth processes. Cadaverine which is the decarboxylation product of lysine has been shown to stimulate the activity of S-adenosyl-methionine decarboxylase and is known to be essential to growth processes of many microorganisms, for example, H. parainfluenza.

SUMM The compounds of general Formula I wherein A is methylene or ethylene are metabolic precursors of compounds having the following structure ##STR18## wherein n is 2 or 3 which are known to be irreversible inhibitors of .gamma.-aminobutyric acid transaminase and upon administration results in higher brain levels of .gamma.-aminobutyric acid (GABA). As precursors of .gamma.-acetylenic-.gamma.-aminobutyric acid the above-described compounds of Formula I are useful in the treatment of disorders of the central nervous system consisting of involuntary movement associated with Huntington's chorea, Parkinsonism, extra-pyramidal effects of drugs, for example, neuroleptics, **seizure** disorders associated with epilepsy, alcohol withdrawal, barbiturate withdrawal, psychoses associated with schizophrenia, depression, manic depression and hyperkinesis.

SUMM That the compounds of general Formula I wherein A is methylene or ethylene and R.sub.2 is hydrogen are converted metabolically to the compounds of Formula II may be demonstrated by the protective effect of the compounds on audiogenic **seizures** in mice of the DBA strain measured by the general method described by Simler et al., Biochem. Pharmacol. 22, 1701 (1973) which is currently used to evidence antiepileptic activity.

PI US 4323704 · 19820406